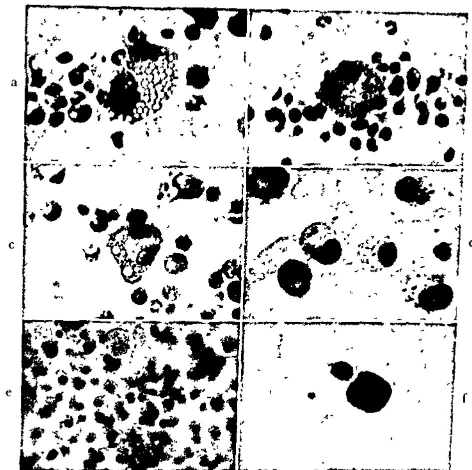
Multiple Myeloma



FRONTISPIECE

Fig. 3.—Myeloma cells containing a variety of cytoplasmic inclusions.

(*a,b*) Large myeloma cells containing numerous rounded bodies which stain blue with Wright's stain.

(*c*) Vacuolated myeloma cell (Mott cell).

(*d*) Cytoplasmic granules produced in myeloma cells after treatment with stilbamidine.

(*e*) Postmortem section of bone marrow stained with H. and E., showing many intra- and extracellular eosinophilic bodies in a patient with multiple myeloma and paramyloidosis. These bodies did not take the stains for amyloid and appear blue with Wright's stain.

(*f*) A large cytoplasmic inclusion staining red with Wright's stain (Russell body).

(Aided in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation.)

Multiple Myeloma

I. SNAPPER, M.D., Director of Medical Education, Cook County Hospital, Chicago, Illinois; Formerly, Director of Medical Education, Mount Sinai Hospital, New York, New York

LOUIS B. TURNER, M.D., Research Assistant in Medicine, Mount Sinai Hospital, New York, New York

HOWARD L. MOSCOVITZ, M.D., Resident, Second Medical Service, Mount Sinai Hospital, New York, New York

Grune and Stratton, New York, 1953

381 Fourth Avenue
New York 16, N. Y.

Printed for Grune & Stratton in the United States of America

CONTENTS

Printed for Grune & Stratton in the United States of America

ACKNOWLEDGEMENTS

We wish to thank our colleagues at The Mount Sinai Hospital who generously gave assistance in the preparation and study of the material for this monograph Dr Donald Kent, Dr Donald Rosenthal, Dr Aaron Freedman, Dr Lee Garlett, Dr Herman Black, and many other members of the House Staff greatly helped in this study

Dr Sadao Otani graciously permitted us to draw from the pathologic material at the hospital Dr Bernard Wolf placed the roentgenologic material at our disposal

We are grateful for the technical assistance of Mr Harry Carlin and Mr Bruno Hein in preparing the illustrations We wish to thank Miss Marcia Kaminsky and Miss June Cobb for the tedious hours they spent in typing the many revisions of the manuscript

INTRODUCTION

Over one hundred years have elapsed since Mac Intyre and Watson attended a highly respectable tradesman with peculiarly fragile bones and urine that was strongly charged with "animal matter" Both physicians were so impressed with the unusual character of this patient's urine that they separately sent specimens to Henry Bence Jones for analysis In 1848[21] Bence Jones described this memorable event in these words:

> "On the 1st of November 1845 I received from Dr Watson the following note, with a test-tube containing a thick, yellow, semi-solid substance — The tube contains urine of very high specific gravity, when boiled it becomes highly opake, on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but as it cools, assumes the consistence and appearance which you now see, heat reliquefies it What is it?"
>
> A few hours afterwards a specimen of the same urine, passed by a grocer forty-seven years of age, who had been out of health for thirteen months, was sent to me by Dr Mac Intyre He being in attendance on the case with Dr Watson had two days previously observed the peculiar reactions of the urine"

Bence Jones then proceeds to describe in detail his careful studies of a "hydrated deutoxide of albumen" which now bears his name Dalrymple[44] published the postmortem findings of this same case in 1846, and Mac Intyre[116] described this case of "Mollities et Fragilitas Ossium" in an admirable report in 1850 These three reports on the same case are the first descriptions we have of the disease which has since been designated multiple myeloma It is remarkable that today, after more than a century of study, much remains to be learned about this disease in general, and the source, chemistry, and constitution of Bence Jones protein in particular

Rustizky,[158] working in von Recklinghausen's laboratory, wrote

INTRODUCTION

Over one hundred years have elapsed since Mac Intyre and Watson attended a highly respectable tradesman with peculiarly fragile bones and urine that was strongly charged with "animal matter." Both physicians were so impressed with the unusual character of this patient's urine that they separately sent specimens to Henry Bence Jones for analysis In 1848[21] Bence Jones described this memorable event in these words

> "On the 1st of November 1845 I received from Dr Watson the following note, with a test-tube containing a thick, yellow, semi-solid substance — 'The tube contains urine of very high specific gravity, when boiled it becomes highly opake, on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but as it cools, assumes the consistence and appearance which you now see, heat reliquefies it What is it?'
>
> [illegible]
>
> urine"

Bence Jones then proceeds to describe in detail his careful studies of a "hydrated deutoxide of albumen" which now bears his name Dalrymple[44] published the postmortem findings of this same case in 1846, and Mac Intyre[116] described this case of "Mollities et Fragilitas Ossium" in an admirable report in 1850 These three reports on the same case are the first descriptions we have of the disease which has since been designated multiple myeloma It is remarkable that today, after more than a century of study, much remains to be learned about this disease in general, and the source, chemistry, and constitution of Bence Jones protein in particular.

Rustizky,[158] working in von Recklinghausen's laboratory, wrote

INTRODUCTION

Over one hundred years have elapsed since Mac Intyre and Watson attended a highly respectable tradesman with peculiarly fragile bones and urine that was strongly charged with "animal matter" Both physicians were so impressed with the unusual character of this patient's urine that they separately sent specimens to Henry Bence Jones for analysis In 1848[21] Bence Jones described this memorable event in these words

> "On the 1st of November 1845 I received from Dr Watson the following note, with a test-tube containing a thick, yellow, semi-solid substance — 'The tube contains urine of very high specific gravity, when boiled it becomes highly opake, on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but as it cools, assumes the consistence and appearance which you now see, heat reliquefies it What is it?'
>
> A few hours afterwards a specimen of the same urine, passed by a grocer forty-seven years of age, who had been out of health for thirteen months, was sent to me by Dr Mac Intyre He being in attendance on the case with Dr Watson had two days previously observed the peculiar reactions of the urine"

Bence Jones then proceeds to describe in detail his careful studies of a "hydrated deutoxide of albumen" which now bears his name Dalrymple[44] published the postmortem findings of this same case in 1846, and Mac Intyre[116] described this case of "Mollities et Fragilitas Ossium" in an admirable report in 1850 These three reports on the same case are the first descriptions we have of the disease which has since been designated multiple myeloma It is remarkable that today, after more than a century of study, much remains to be learned about this disease in general, and the source, chemistry, and constitution of Bence Jones protein in particular

Rustizky,[153] working in von Recklinghausen's laboratory, wrote

the first definitive pathologic description of this disease in 1873 and proposed the name of myeloma for the condition However, it was not until the appearance of Kahler's article in 1889,[90] almost forty years after the original paper, that the disease became generally known. Kahler is given credit for recognizing that the association of deformity and abnormal fragility of the bones, bone pain, cachexia, and the presence of Bence Jones protein in the urine almost always indicated the presence of multiple myeloma. Today multiple myeloma is still often referred to as Kahler's disease.

The introduction of radiology into medicine then gave great impetus to our understanding of this disease and has greatly facilitated its diagnosis. It was soon recognized that on x-ray examination the typical myelomatous bone lesion consists of a sharply delineated osteolytic area without accompanying bone proliferation or sclerosis It also became apparent that in certain cases the entire bone marrow could be involved by a diffuse myelomatous process without the formation of tumor-like plasmocytomas. In such cases circumscribed roentgenologic lesions are not visible and the picture is characterized only by a generalized demineralization of the skeleton

New concepts of the etiology of multiple myeloma have gradually developed It was originally thought that myeloma, as the name implies, was merely a tumor, usually a plasmocytoma, derived from elements of the bone marrow In recent years many students of the disease have become convinced that myeloma is not a neoplasm in the usual sense of the word Some clinicians consider myeloma to be the aleukemic phase of plasma cell leukemia [113] Numerous clinical and experimental observations have emphasized the close relationship existing between myeloma, leukemia, and certain diseases of the reticuloendothelial system.[149,166] For example, in multiple myeloma, abnormal cells are often present in the peripheral blood, occasionally in such large numbers as to present the picture of plasma cell leukemia. On the other hand, in both the myeloid and lymphatic leukemias, tumor formations, though rare, are known to occur. Furthermore, as is the rule in leukemia, certain cases of myeloma exhibit a diffuse proliferation of abnormal cells in the bone marrow without localized tumor formation Experimental evidence of a relationship between multiple myeloma and leukemia has also been presented. Furth[63] has demonstrated that both leukemia and tumors resembling myelomas develop in mice injected with a cell suspension of a transmissible

strain of myeloid leukemia. Thus, regardless of its skeletal or local onset, there is much to be said for including multiple myeloma among the generalized proliferative disorders of the reticuloendothelial system

In recent years many studies have been made of the characteristic changes of protein metabolism which are found in multiple myeloma in the hope that they might shed light on the etiology of the disease *Three major aberrations of protein metabolism are known to occur* in multiple myeloma. The first is the excretion of Bence Jones protein, which is present in the urine of about 50 per cent of the cases of multiple myeloma This remarkable protein is virtually pathognomonic of multiple myeloma because it is only rarely, if ever, found in other diseases Almost as characteristic is the increase of the serum globulin found in 60 per cent of myeloma patients Although there are many other diseases where the globulin content of the serum is increased, the globulin fractions in multiple myeloma, as determined by Howe fractionation or electrophoretic analysis, have certain characteristics which are not present in other diseases with hyperglobulinemia

Finally, paramyloidosis, the least common and least understood of the protein anomalies of multiple myeloma, occurs in about 10 per cent of the patients In myeloma, deposits of this peculiar protein are usually found in the walls of blood vessels, between the muscle fibers of tongue, heart, and gastrointestinal tract, in the capsules of joints, and in other mesenchymal tissues In contrast, the amyloid which develops after long-standing suppuration is deposited in the spleen, liver, kidneys, adrenals, and also in blood vessel walls An inverse relationship seems to exist between hyperglobulinemia and paramyloid deposition, since in myeloma cases with paramyloid, hyperglobulinemia is infrequent In contrast, nearly all myeloma patients with paramyloidosis have Bence Jones proteinuria The recognition of these bizarre metabolic abnormalities lends weight to the concept that multiple myeloma is no mere bone tumor and could logically be included among the diseases of metabolism

Waldenstrom,[199–201] and later Dent and Rose,[48,49] have voiced the opinion that abnormal proteins present in multiple myeloma could conceivably result from an infection with a virus Citing the analogous observation of the tobacco mosaic virus, in which the proteins of the plant are gradually replaced by the proteins of the virus, Walden-

ström speculates that the immature plasma cells invaded by a virus might form the abnormal globulins found in multiple myeloma. The fact that they could find no methionine in their analysis of Bence Jones protein led Dent and Rose to the conclusion that this substance was more likely to be produced by a virus than by cellular metabolism. It has further been surmised that the basophilic, stilbamidine-containing granules in myeloma cells which appear after injections of stilbamidine may have a bearing upon this problem [49] It may be that in the myeloma cells tiny particles of nucleoprotein are present which cannot be visualized by the usual staining technics, but which can be demonstrated by the precipitation of stilbamidine upon such particles Since viruses consist of small particles of nucleoproteins, there has been speculation that perhaps stilbamidine serves to render visible the virus present in myeloma cells

All this is, however, pure hypothesis and for the time being the nature and pathogenesis of multiple myeloma remain completely unknown In the absence of a proven etiologic agent, our knowledge can only be furthered by repeated and careful clinical observation and study In this way it may be possible to obtain sufficient data to test the different possibilities In recent years several extensive review articles have been written Walgren[205] in 1921, collected all the observations recorded in the literature in an excellent monograph. Geschickter and Copeland[66] reviewed four hundred twenty-five cases reported before 1928 and added thirteen cases of their own. Atkinson[13] wrote a review in the British literature in 1937 In 1947 Bayrd and Heck[19] reviewed eighty-three cases seen at the Mayo Clinic Lichtenstein and Jaffe[105] reported on thirty-five cases including eighteen autopsies and Adams, Alling, and Lawrence,[1] in 1949, reported on sixty-one cases. Many of these reviews are compilations of cases, most of which were not personally observed by the authors.

During the past seven years we have had the unusual opportunity to study personally in the wards of the Mt. Sinai Hospital ninety-seven cases of multiple myeloma, forty-one of which have come to autopsy These ninety-seven cases, combined with personal observations made on other patients, form the material on which this report is based.

1. THE MYELOMA CELL

In 1900, Wright[214] first drew attention to the similarity between the Marschalko plasma cell and the offending marrow elements of multiple myeloma and in 1907, Henry Christian[34] confirmed this finding in six cases of his own. Arinkin[10] first described the technic of bone marrow aspiration in 1929, but it was not until 1936 that this technic came into general use in the study of multiple myeloma. Its value for the diagnosis of myeloma was emphasized in 1938 by Rosenthal and Vogel,[151] who pointed out that, despite the roentgen picture suggesting focal, discrete, disseminated lesions, the marrow is usually universally involved and because of this diffuse plasmocytosis, a marrow aspiration, even at some distance from an osteolytic lesion, is usually positive.

Before the use of marrow aspiration became general, a great deal of confusion had arisen from cytologic studies of microscopic tissue sections. Erf and Herbert[59] and Wintrobe[211] have pointed out that in such sections histologic detail of cytoplasm and nucleus is greatly inferior to that which can be obtained from smears of a marrow aspiration. Formerly it was a widely held concept that many, if not all, types of marrow cells could be responsible for the syndrome of multiple myeloma. Thus, there were numerous reports on lymphoblastic,[197] erythroblastic,[197] plasmocytic, myeloblastic,[166,197] myelocytic,[151] megakaryoblastic,[59,69] and osteoblastic[209] types of multiple myeloma. Even a myeloma mixtocellulare arising from the proliferation of two different bone marrow elements was described. Since the advent of marrow aspiration studies, these reports have become scarce and nearly all cases of myeloma seem to belong to the plasmocytoma group.

Bayrd,[18] after reviewing a large series of myeloma marrows at the

strôm speculates that the immature plasma cells invaded by a virus might form the abnormal globulins found in multiple myeloma. The fact that they could find no methionine in their analysis of Bence Jones protein led Dent and Rose to the conclusion that this substance was more likely to be produced by a virus than by cellular metabolism. It has further been surmised that the basophilic, stilbamidine-containing granules in myeloma cells which appear after injections of stilbamidine may have a bearing upon this problem [49] It may be that in the myeloma cells tiny particles of nucleoprotein are present which cannot be visualized by the usual staining technics, but which can be demonstrated by the precipitation of stilbamidine upon such particles. Since viruses consist of small particles of nucleoproteins, there has been speculation that perhaps stilbamidine serves to render visible the virus present in myeloma cells

All this is, however, pure hypothesis and for the time being the nature and pathogenesis of multiple myeloma remain completely unknown In the absence of a proven etiologic agent, our knowledge can only be furthered by repeated and careful clinical observation and study In this way it may be possible to obtain sufficient data to test the different possibilities In recent years several extensive review articles have been written. Walgren[205] in 1921, collected all the observations recorded in the literature in an excellent monograph Geschickter and Copeland[66] reviewed four hundred twenty-five cases reported before 1928 and added thirteen cases of their own Atkinson[13] wrote a review in the British literature in 1937 In 1947 Bayrd and Heck[19] reviewed eighty-three cases seen at the Mayo Clinic. Lichtenstein and Jaffe[105] reported on thirty-five cases including eighteen autopsies and Adams, Alling, and Lawrence,[1] in 1949, reported on sixty-one cases Many of these reviews are compilations of cases, most of which were not personally observed by the authors

During the past seven years we have had the unusual opportunity to study personally in the wards of the Mt. Sinai Hospital ninety-seven cases of multiple myeloma, forty-one of which have come to autopsy. These ninety-seven cases, combined with personal observations made on other patients, form the material on which this report is based

1. THE MYELOMA CELL

In 1900, Wright[214] first drew attention to the similarity between the Marschalko plasma cell and the offending marrow elements of *multiple myeloma* and in 1907, *Henry Christian*[31] *confirmed* this finding in six cases of his own. Arinkin[10] first *described* the technic of bone marrow aspiration in 1929, but it was not until 1936 that this technic came into general use in the study of multiple myeloma. Its value for the diagnosis of myeloma was emphasized in 1938 by Rosenthal and Vogel,[151] who pointed out that, despite the roentgen picture suggesting focal discrete, disseminated lesions, the *marrow* is usually *universally* involved *and* because of this diffuse plasmocy*tosis, a marrow* aspiration, *even* at some distance *from an* osteolytic lesion, is usually positive.

Before the use of marrow aspiration became general, a great deal of confusion had arisen from cytologic studies of microscopic tissue sections. Erf and Herbert[59] and Wintrobe[211] have pointed out that in such sections histologic detail of cytoplasm and nucleus is greatly inferior to that which can be obtained from smears of a marrow aspiration. Formerly it was a widely held concept that many, if *not* all, types of *marrow cells could* be *responsible for* the syndrome of multiple *myeloma*. Thus, there were *numerous reports on* lymphoblastic,[197] erythroblastic,[197] plasmocytic, myeloblastic,[146,197] myelocytic,[121] megakaryoblastic,[59,69] and osteoblastic[209] types of multiple myeloma. Even a myeloma mixtocellulare arising from the proliferation of two different bone marrow elements was described. Since the advent of marrow aspiration studies, these reports have become scarce and nearly all cases of myeloma seem to belong to the plasmocytoma group.

Bayrd,[13] after reviewing a large series of myeloma marrows at the

Mayo Clinic, concluded that all cases were of the plasma cell type In his material, the myeloma plasma cell constituted 2.5 to 96 per cent of the cellular elements of the bone marrow. In our series the percentage of myeloma cells in marrow aspirates also varied from 2 to 3 per cent on up to 90 per cent It appears probable that all of the so-called different types of multiple myeloma are merely variations in differentiation of the same cell type There is even a tendency

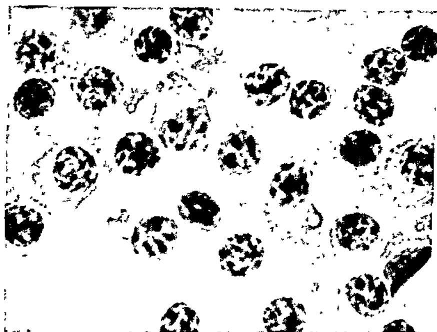


FIG 1 —Sheets of mature myeloma cells in bone marrow aspirate showing the *characteristic clumping of chromatin in the nucleus*

among students of this disease to replace the term myeloma by the designation plasmocytoma Most clinicians follow Wallgren's[205] suggestion that the name myeloma cell be used for the designation of *the abnormal cell which we have come to identify with the disease* myeloma

The myeloma cell varies from a small, mature, dark blue, almost characteristic plasma cell (fig 1) to an immature, anaplastic, large cell 20 to 40 μ in diameter Although there is occasionally a marked degree of pleomorphism, it is more common to find a monotonous uniformity in the staining qualities, texture, and size of the myeloma cells in the marrow aspirate from any given case The large cell type

has a pale blue cytoplasm, rather frequently containing vacuoles or other inclusions. The mature cells with dark blue cytoplasm, on the other hand, rarely contain inclusions. Both types may exhibit a fine azurophilic granulation of the cytoplasm. Sandkühler[161,162] found such azurophilic granulations in two patients who demonstrated an alpha globulin peak on electrophoretic analysis. In our material this azurophilic granulation was also found in the myeloma cells of patients with other electrophoretic patterns.

The nucleus of the myeloma cell has certain distinctive features. An outstanding characteristic is its eccentric position in the cell. The nucleus, usually measuring 5 to 7 μ in diameter, presents a closely knit, reticulated appearance with the chromatin often present in small sausage-like clumps (fig. 1). The blocky, wheel-spoke arrangement of chromatin which characterizes the plasma cell is hardly ever encountered in myeloma cells as they are seen in bone marrow smears Younger forms with a more vesicular nucleus, in which the chromatin is evenly distributed and arranged in a fine network, are also frequently seen. The nucleus often contains one large nucleolus, occasionally 2 to 4 nucleoli A prominent perinuclear halo is frequently present Multinucleated forms occur commonly and probably represent the large giant cells seen on tissue section (fig 2). The more immature myeloma cells contain large, sometimes lobulated nuclei, occasionally with a giant nucleolus.

Peculiar cytoplasmic inclusions have been described by many authors and have been the subject of much study and speculation (frontispiece—fig 3) The cytoplasm may contain rather large fuchsinophilic or acidophilic inclusions (frontispiece—fig 3f), which have been called Russell bodies because of their similarity to the fuchsin bodies which were described, in 1890, by William Russell[157] as the "characteristic organisms of cancer." Russell was of the opinion that these fuchsinophilic inclusions represented fungi which might conceivably be the cause of the carcinomatous degeneration of body cells Similar inclusions have since been found to occur frequently in the cells of the digestive tract of animals and in the lymph nodes of rats and guinea pigs [140] Recently, Lisco[108] studied their occurrence in the intestinal tract of pigs. He found the cytoplasm of the intestinal epithelial cells at times so crowded with these eosinophilic bodies that at first glance the cytoplasm appeared to consist solely of red staining material On careful examination it could then be seen that the

Mayo Clinic, concluded that all cases were of the plasma cell type. In his material, the myeloma plasma cell constituted *2.5 to 96 per cent* of the cellular elements of the bone marrow. In our series the percentage of myeloma cells in marrow aspirates also varied from 2 to 3 per cent on up to 90 per cent. It appears probable that all of the so-called different types of multiple myeloma are merely variations in differentiation of the same cell type. There is even a tendency

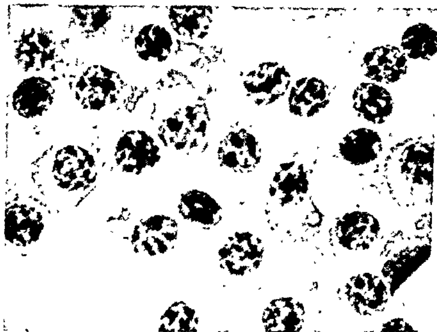


Fig. 1.—Sheets of mature myeloma cells in bone marrow aspirate showing the characteristic clumping of chromatin in the nucleus.

among students of this disease to replace the term myeloma by the designation plasmocytoma. Most clinicians follow Wallgren's[204] suggestion that the name myeloma cell be used for the designation of the abnormal cell which we have come to identify with the disease myeloma.

The myeloma cell varies from a small, mature, dark blue, almost characteristic plasma cell (fig. 1) to an immature, anaplastic, large cell 20 to 40 μ in diameter. Although there is occasionally a marked degree of pleomorphism, it is more common to find a *monotonous uniformity* in the staining *qualities, texture,* and *size* of the myeloma cells in the marrow aspirate from any given case. The large cell type

The vacuoles which may be present in myeloma cells, forming the so-called Mott cells[23] (frontispiece—fig 3a,b,c), are sometimes mistakenly called Russell bodies This confusion may be traced to the fact that Russell bodies, because of their protein content, stain blue with Weigert stain, and that occasionally such blue staining material has also been found in the vacuoles of Mott cells. However, with Romanofsky stains (Giemsa or Wright stains), Russell bodies which are fuchsinophilic and eosinophilic appear red while the vacuoles are either clear or may rarely contain greyish-blue material Despite their different staining qualities, both structures probably represent abnormal proteins formed by the myeloma cell Cytochemical studies of the nature of Russell bodies have been carried out by Pearse,[140] who concludes that they consist of mucoprotein They are not affected by ribonuclease, and they are not metachromatic. Downey[50] regards Russell bodies as pathologic secretions or as aggregates of normal secretions found in the parent plasma cell He feels that the bodies are liberated into the tissues following the death of the parent cell

At times, large crystals can be found in myeloma cells and also in the renal tubular epithelial cells of patients with Bence Jones proteinuria It appears that these crystals are also protein in nature since Apitz[8] has reported that they stain blue with the Weigert stain. This author, and later Kabelitz,[89] emphasized that neither these protein crystals nor the vacuoles mentioned above are pathognomonic for myeloma cells since such crystals and vacuoles, staining blue with Weigert stain, can be found in normal plasma cells. Pseudopod-like cytoplasmic extrusions are often present. Such fragments of the cytoplasm break off easily and are then found as isolated bluish masses all through the bone marrow smear

Not only is the etiology of multiple myeloma still completely obscure, but the origin of the myeloma cell is the subject of widely varying interpretations For many decades it was generally accepted that plasma cells were derived from lymphocytes, especially since Maximow demonstrated that plasma cells can be produced in culture by explants of lymphoid tissue Other ideas as to the origin of the plasma cells were, until recently, based on microscopic studies of tissue sections obtained at autopsy or biopsy Wintrobe[211] believes that the myeloma cell is a type unto itself, differing from all other cells, Klemperer,[93] Churg and Gordon,[37] and Lowenhaupt,[111] on the other hand, have emphasized that the cells forming both the medullary and

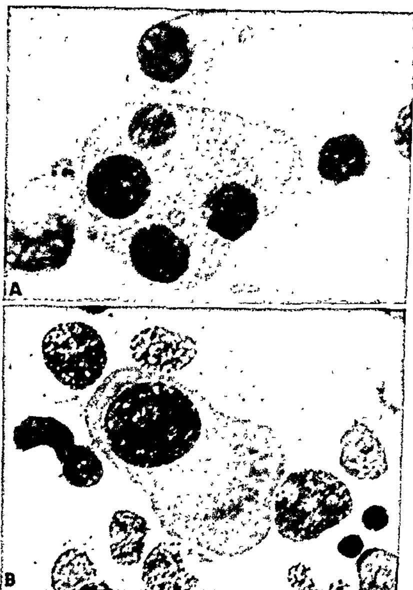


FIG 2 —(*a*) Bizzare, quadrinucleate myeloma cell (*b*) Giant myeloma cell

cytoplasm of the cells was actually packed with eosinophilic inclusions Some observers are of the opinion that these Russell bodies occur only in plasma cells; others have seen them also in lymphocytes At any rate, the presence of Russell bodies is not diagnostic of multiple myeloma

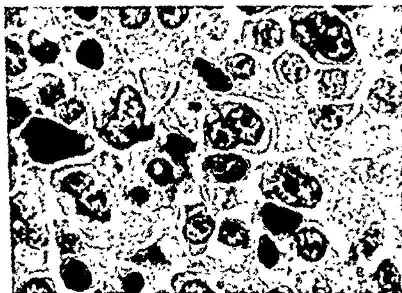


Fig. 4.—(*a*) Section of myelomatous *tumor* arising from iliac wing The cells resemble mature myeloma cells (*b*) Section of lymph node from same patient (H C) as *a* The cells have large clear vesicular *nuclei closely* resembling those found in reticulum cell sarcoma

the extramedullary plasmocytomas may well be derived from the reticulum cell

Analysis of the bone marrow smears of our patients revealed in most cases myeloma cells with sausage-like arrangement of the chromatin of the nucleus as described above. Usually one large nucleolus was present, occasionally more In several cases it was possible to find myeloma cells which were predominately of a reticulum cell type in some areas and of a plasma cell type in other areas (fig 4a,b). There were also cases in which plasmocytomas consisted only of cells with very loosely knit nuclei without nucleoli; these could only be designated as reticulum cells The latter finding seems to lend support to the hypothesis that myeloma cells are derived from reticulum cells Lowenhaupt[111] has reported that in patients with multiple myeloma, examination of the spleen usually reveals a proliferation of myeloma cells in the splenic sinuses Often myeloma cells replace the endothelial lining of the sinuses and one obtains the impression that the myeloma cells are derived from these lining cells, which actually represent the reticulum cells of the hemopoietic organs Thus, it is now generally believed that the myeloma cell is a derivative of the reticulum cell, rather than a descendent of the lymphoid series

In the great majority of our cases, the marrow involvement was generalized despite the apparent x-ray appearance of sharply localized and discrete areas of bone destruction Marrow aspiration made anywhere, whether it be from the sternum, iliac crest, ribs, or vertebral spine, was usually productive of myeloma cells In exceptional cases either repeated marrow aspirations were necessary or positive smears could be obtained only from one particular area. In such cases the proliferation of myeloma cells must have been patchy in character. This difficulty is encountered in cases which have multiple plasmocytomas without generalized myelomatosis of the marrow, and which usually have a less acute course than the classical cases of multiple myeloma (p 103). This was true of a patient with a pathologic fracture of the femur, with lytic lesions in the skull, spine, humeri, and ribs, in whom myeloma cells could only be found at the fracture site and never in the marrow obtained by puncture of sternum, iliac crest, or ribs.

Plasmocytomas are often hemorrhagic In such cases the material obtained by bone marrow puncture may be so diluted with peripheral blood that the bone marrow smear does not permit a diagnostic

A

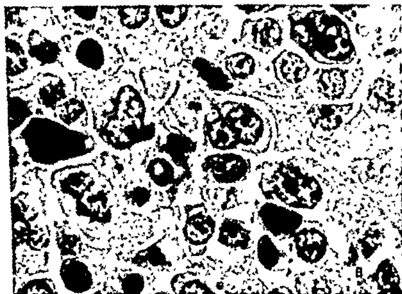


Fig 4.—(*a*) Section of myelomatous tumor arising from iliac wing The cells resemble mature myeloma cells (*b*) Section of lymph node from same patient (H C) as *a* The cells have large clear vesicular nuclei, closely resembling those found in reticulum cell sarcoma.

statement. In that event a bone marrow biopsy may be necessary in order to arrive at a correct diagnosis. Although part of the histologic details of cytoplasm and nuclei of the myeloma cells are lost in the microscopic sections, the monotonous arrangement of the proliferating cells, the scarcity of pleomorphism, and the scanty stroma are typical.

Several observers have reported[18,217] that the prognosis for longevity in any given case is generally related to the degree of maturity of the myeloma cells in the marrow, with the poorest prognosis assigned to the patients with the most immature type of cell. We have not been able to convince ourselves that this holds true in the group of patients we observed. Léger and his associates[102a] also were unable to find a correlation between the cytologic characteristics of the myeloma cells and the clinical development of the disease.

It should be emphasized that the morphologically distinct character of the myeloma cell is of great diagnostic importance since a nonmyelomatous infiltration of the bone marrow with mature plasma cells occurs rather frequently. Such a plasmocytosis of the marrow may be found in all diseases in which hyperglobulinemia is common such as lupus erythematosus, Boeck's sarcoidosis, liver cirrhosis, kala-azar, lymphopathia venereum, etc. Finally, large numbers of plasma cells with mature, somewhat pycnotic nuclei are nearly always found in the bone marrow of patients with agranulocytosis Only the presence of a significant number of cells with the distinctive characteristics of the myeloma cell, especially when they occur in groups or sheets, indicates the presence of multiple myeloma.

2. INCIDENCE AND SURVIVAL

Although the disease may occur at almost any age, the majority of cases occur between the ages of 50 and 70 years In 66 per cent of our cases, the onset of recognizable symptoms started during that period and 95 per cent of the patients were over the age of 40 years (fig. 5). Multiple myeloma has been

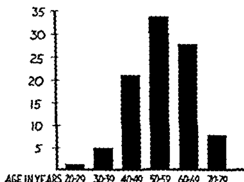


Fig 5 —Distribution of cases according to age of onset of symptoms

observed in patients below 20 years.[22] In this series the youngest patient was 29 years old, whereas the oldest was 76. The preponderance of the disease in males is well established, and in this series 65 per cent of the ninety-seven patients were men. Eight Negroes are included, reflecting approximately the proportion of Negro patients on the medical wards No apparent relationship of multiple myeloma to occupation, income class, or to living conditions could be recognized

Multiple myeloma is universally fatal with a poor prognosis as to length of life after the onset of symptoms (fig. 6). In some cases, where pain is not prominent, it is difficult to designate the date of onset of

symptoms and some such cases had to be dated back to the apparent time of onset of progressive weight loss, weakness, and fatiguability, or to the first of several recurrent pneumonias. In the cases reviewed in the literature the average time between initial symptoms and death is usually given as one and a half to two years. It can be seen from

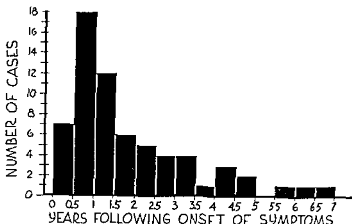


FIG 6—Duration of life after onset of symptoms in the fifty-five patients who have died

figure 2 that in the group of sixty-four cases who have already died, the average duration of life was twenty months However, the majority of our cases lived less than one and a half years after the onset of symptoms In our series, the duration has varied from so short a period as nine weeks to a period of over eight years Rare cases have been reported with even longer survivals [65 91]

One such case which we observed has been described in detail elsewhere.[178]

A 43 year old woman entered the Mount Sinai Hospital in 1946 At this time she already had a two year history of bone pains *She had typical multiple myeloma*, with widespread involvement of the skeleton The serum albumin and globulin concentrations were normal, but a small amount of Bence Jones protein was present in the urine She received three courses of stilbamidine, totalling 7 5 Gm in the course of one and a half years

At a follow-up clinic in March, 1951, seven years after the onset of her disease, the following note was written "Remarkable remission continues Patient is ambulatory and was able to dance at her son's wedding on Janu-
... confined
... changes
... probably
due to severe amyloid involvement of the joint capsules since a biopsy of an egg-sized nodule located in the left ischial bursa revealed the presence of amy-

loid The iliac marrow still contained sheets of myeloma cells (fig 1) The urine, as before, contained Bence Jones protein, but after six years of Bence Jones proteinuria there was only mild renal insufficiency, the blood urea nitrogen being 24 mg per cent and the PSP excretion 40 per cent in two hours The serum globulin determined by the Howe fractionation method had been normal throughout the entire eight years of disease (table 1) (This patient ultimately died in the first part of 1953.)

TABLE 1.—*Serum Proteins in a Patient with Multiple Myeloma Still Alive Eight Years after the Onset of the Disease*

Date	Total protein	Albumin	Globulin
4/1/46	5.8	3.9	1.9
4/28/46	7.5	4.5	3.2
5/27/46	6.8	5.1	1.7
6/7/46	6.0	4.5	1.5
12/2/46	7.4	5.3	2.1
1/6/47	8.5	6.0	2.5
3/21/47	6.5	5.2	1.3
10/6/47	5.4	3.6	1.8
10/11/47	7.4	4.9	2.5
9/17/51	7.1	4.5	2.6
9/11/52	7.1	4.4	2.6
9/16/52	5.6	3.5	2.1

3. THE PERIPHERAL BLOOD PICTURE

One of the most common findings in patients with multiple myeloma is anemia, and not infrequently it may be the only obvious sign of the disease It is usually *moderately* severe, and in this series red blood cell counts ranged between 2,000,-000 and 4,000,000 per cu mm and hemoglobin determinations between 6 and 10 Gm. per cent It is difficult to be more exact since the anemia usually became slowly but progressively more severe, and many patients received multiple transfusions Four patients had normal red cell counts and hemoglobin levels Lawrence and Rosenthal[102] reported four cases of polycythemia associated with multiple myeloma In the series of ninety-seven hospitalized myeloma patients reviewed here no case showed polycythemia We have, however, followed, for the last four years, one additional out-patient with multiple plasmocytomas who, for some time, did have a moderate polycythemia (p 104)

In 20 per cent of these cases a leukocytosis was present and in 40 per cent a leukopenia was noted Leukopenia was often observed to develop in the later stages of the disease in many patients who presented, initially, a normal white count or even a leukocytosis. This occurred even in patients who did not receive radiotherapy or drugs, such as urethane, which tend to reduce the total leukocyte count.

The differential white cell count is usually unremarkable although 50 per cent of the cases showed a moderate shift to the left. A totally unexplained eosinophilia occurred in three cases in this series, where the eosinophil count was noted to be 46 per cent, 32 per cent, and 20 per cent respectively, without overt evidence of an allergic state or infestation with parasites Eosinophilia in multiple myeloma has also been noted by others [9,211] Plasma cells were found in the peripheral

blood in 22 per cent of the cases Five patients had between 15 and 40 per cent plasma cells in the blood Four of these five patients, at autopsy, had a leukemic type of infiltration of the liver, spleen, and lymph nodes with large numbers of plasma cells. These four cases with marked plasma cell invasion of the peripheral blood, accompanied by thrombocytopenia and severe anemia, may be classified as instances of plasma cell leukemia, first described by Gluzinski and Reichenstein [63] Plasma cell leukemia is a rare occurrence. Danish authors report that in their material, for every case of plasma cell leukemia, fifty cases of multiple myeloma and two hundred and fifty cases of myeloid and lymphatic leukemia are observed [27] It should be noted that in many, but by no means all, cases of plasma cell leukemia with myelomatosis of the bone marrow, the roentgenologic manifestations of the disease have been minimal It seems that invasion of the peripheral blood by myeloma cells occurs much more frequently in patients with diffuse myelomatosis than in cases where tumor-like plasmocytomas develop Majeranowski[119] has recently suggested that plasma cell leukemia without roentgenologic skeletal lesions and without hyperglobulinemia should be classified separately from multiple myeloma with plasma cell invasion of the peripheral blood. Since transitions between multiple plasmocytomas, diffuse myelomatosis of the bone marrow, and plasma cell leukemia are found, this differentiation does not seem justified We agree with the general concept that plasma cell leukemia is merely a variant of multiple myeloma, in which large numbers of plasma cells reach the peripheral blood stream Diffuse plasma cell infiltration of the viscera may also occur without invasion of the peripheral blood by plasma cells.[36, 186]

Although only 22 per cent of the cases showed plasma cells in the peripheral blood smears, many other cases were found to have atypical mononuclear cells which may well have been variants of the myeloma cells seen in the marrow If smears are made of the buffy coat of myeloma blood, plasma cells may be found in almost every case As the anemia becomes increasingly severe, it is not unusual for normoblasts to appear in the blood A leukoerythroblastic picture was seen in 10 per cent of the cases and probably reflects the myelophthisic process produced by space occupying myelomatous tissue Invasion of the peripheral blood by myelocytes and erythroblasts is, therefore, usually a preterminal sign Thrombocytopenia with platelet counts under 100,000 as described by Rosenthal and Vogel[151] occurred in

3. THE PERIPHERAL BLOOD PICTURE

One of the most common findings in patients with multiple myeloma is anemia, and not infrequently it may be the only obvious sign of the disease. It is usually moderately severe, and in this series red blood cell counts ranged between 2,000,000 and 4,000,000 per cu mm and hemoglobin determinations between 6 and 10 Gm. per cent It is difficult to be more exact since the anemia usually became slowly but progressively more severe, and many patients received multiple transfusions. Four patients had normal red cell counts and hemoglobin levels. Lawrence and Rosenthal[102] reported four cases of polycythemia associated with multiple myeloma In the series of ninety-seven hospitalized myeloma patients reviewed here no case showed polycythemia We have, however, followed, for the last four years, one additional out-patient with multiple plasmocytomas who, for some time, did have a moderate polycythemia (p 104)

In 20 per cent of these cases a leukocytosis was present and in 40 per cent a leukopenia was noted Leukopenia was often observed to develop in the later stages of the disease in many patients who presented, initially, a normal white count or even a leukocytosis. This occurred even in patients who did not receive radiotherapy or drugs, such as urethane, which tend to reduce the total leukocyte count

The differential white cell count is usually unremarkable although 50 per cent of the cases showed a moderate shift to the left. A totally unexplained eosinophilia occurred in three cases in this series, where the eosinophil count was noted to be 46 per cent, 32 per cent, and 20 per cent respectively, without overt evidence of an allergic state or infestation with parasites. Eosinophilia in multiple myeloma has also been noted by others.[6,211] Plasma cells were found in the peripheral

blood in 22 per cent of the cases. Five patients had between 15 and 40 per cent plasma cells in the blood. Four of these five patients, at autopsy, had a leukemic type of infiltration of the liver, spleen, and lymph nodes with large numbers of plasma cells. These four cases with marked plasma cell invasion of the peripheral blood, accompanied by thrombocytopenia and severe anemia, may be classified as instances of plasma cell leukemia, first described by Gluzinski and Reichenstein[68] Plasma cell leukemia is a rare occurrence. Danish authors report that in their material, for every case of plasma cell leukemia, fifty cases of multiple myeloma and two hundred and fifty cases of myeloid and lymphatic leukemia are observed.[27] It should be noted that in many, but by no means all, cases of plasma cell leukemia with myelomatosis of the bone marrow, the roentgenologic manifestations of the disease have been minimal. It seems that invasion of the peripheral blood by myeloma cells occurs much more frequently in patients with diffuse myelomatosis than in cases where tumor-like plasmocytomas develop. Majeranowski[119] has recently suggested that plasma cell leukemia without roentgenologic skeletal lesions and without hyperglobulinemia should be classified separately from multiple myeloma with plasma cell invasion of the peripheral blood Since transitions between multiple plasmocytomas, diffuse myelomatosis of the bone marrow, and plasma cell leukemia are found, this differentiation does not seem justified We agree with the general concept that plasma cell leukemia is merely a variant of multiple myeloma, in which large numbers of plasma cells reach the peripheral blood stream. Diffuse plasma cell infiltration of the viscera may also occur without invasion of the peripheral blood by plasma cells.[36,186]

Although only 22 per cent of the cases showed plasma cells in the peripheral blood smears, many other cases were found to have atypical mononuclear cells which may well have been variants of the myeloma cells seen in the marrow If smears are made of the buffy coat of myeloma blood, plasma cells may be found in almost every case. As the anemia becomes increasingly severe, it is not unusual for normoblasts to appear in the blood A leukoerythroblastic picture was seen in 10 per cent of the cases and probably reflects the myelophthisic process produced by space occupying myelomatous tissue Invasion of the peripheral blood by myelocytes and erythroblasts is, therefore, usually a preterminal sign Thrombocytopenia with platelet counts under 100,000 as described by Rosenthal and Vogel[151] occurred in

25 per cent of our patients Bayrd and Heck[19] did not observe cases of thrombopenia among their cases.

Associated frequently with hyperglobulinemia, but also occurring in its absence, is a marked tendency toward rouleau formation of the red cells, clumping of red cells in Hayem's solution and the formation of a bluish cast or sheen to the stained blood smear. Because of this latter characteristic, the laboratory technician may be the first to suggest to the clinician the diagnosis of the myeloma. The relationship between the rouleau formation, rapid sedimentation rate, and elevated serum globulins was noted by Fahraeus in 1921.[61] The tendency to autohemaglutination of red cells in myeloma has been described by Reimann[144] and others, and frequently it makes cross-matching of the blood exceedingly difficult. When this occurs, cross-matching in an incubator kept at 28 C. is necessary.

Rapid erythrocyte sedimentation rate is a characteristic finding in myeloma However, ten of ninety-seven consecutive patients had a sedimentation rate below 20 mm per hour by the Westergren method at one stage of the disease None of these cases had an elevation of the serum globulin (table 2). It can be predicted that the sedimentation rate will be excessively high, often over 150 mm. per hour, if the serum globulin is elevated However, it should be emphasized that an increase of the plasma fibrinogen augments the sedimentation rate of the red cells even more than an increase of the serum globulin Thus, the sedimentation rate may be high even though the serum globulin concentration is normal. The important point remains that an occa-

TABLE 2 —*Serum Concentrations of Albumin and Globulin in Ten Patients with Sedimentation Rates below 20 mm /hr*

Case	Erythrocyte sedimentation rate mm /hr	Serum albumin Gm %	Serum globulin Gm %
4	6	3 2	1 8
10	5	4 5	1 5
12	4	4 5	1 2
24	20	4 9	1 5
28	12	4 2	1 5
47	12	4 2	3 0
50	10	4 3	2 3
63	5	4 6	1 6
67	6	2 6	1 9
77	12	5 2	1 2

sional case of multiple myeloma with low or normal serum globulin concentration will have a sedimentation rate below 20 mm. per hour. Many of these cases represented the more difficult diagnostic problems in this series.

Hemorrhagic Tendency

An unusual bleeding tendency was found in thirty-two (35 per cent) of the cases Eleven patients had repeated epistaxes and seven noted bleeding gums of moderate degree. Eight patients had hemoptysis, three had grossly bloody stools, eight had retinal hemorrhages, and three demonstrated numerous petechiae and purpuric hemorrhages in the skin. Although these bleeding phenomena were occasionally associated with thrombocytopenia, increased capillary fragility, prolonged clotting time or poor clot retraction, this was not the general rule

Goltz[68b] emphasizes that in systematized amyloidosis or paramyloidosis, hemorrhages in the skin are very frequently observed The purpura in paramyloid results from damage of the walls of the cutaneous blood vessels by infiltration with amyloid. Since paramyloid is frequently observed in multiple myeloma, it is not unlikely that unexplained hemorrhagic skin lesions may occasionally be due to vascular amyloid Cryoglobulins were sought for in seventeen cases of unexplained bleeding, but were found in only one case It is noteworthy that in our series, myeloma patients with a hemorrhagic tendency, like myeloma patients with recurrent pneumonia, demonstrated a higher incidence of elevated serum globulins than the average patient without bleeding tendency

Macroglobulinemia

Waldenstrom[201,202] has observed, in Sweden, a hemorrhagic syndrome which he terms "macroglobulinemia" It is characterized by lassitude, dyspnea, anemia, bleeding from the gums, and purpura. Bone pains are minimal, x-ray examination reveals only demineralization of the bones, and marrow aspiration reveals the presence of large numbers of "lymphocytoid cells with shedding of protoplasm." Hyperglobulinemia is present, but it differs from that seen in multiple myeloma in that a predominant increase in globulins of high molecular weight (S 20 component) is found on the ultracentrifugation of serum (p 84). Electrophoretically, these pathologic macroglobulins

behave like beta or gamma globulins. These sera usually give a strong euglobulin reaction with the sodium sulfate fractionation, but Bichel, Bing, and Harboe[26] describe one case of macroglobulinemia in which the euglobulin reaction was negative Cases with macroglobulinemia, fever, and central nervous system degeneration (paresis, increase of globulin in the spinal fluid) have also been described [26] The complete syndrome as described by Waldenstrom was not seen in any of the cases in the present series. In those of our cases which were complicated by purpura or excessive bleeding, none had simple demineralization on x-ray examination. All but two had multiple osteolytic lesions, and these two had no demonstrable lesions at all. Of five myeloma patients with generalized demineralization of the bone but no discrete lytic lesions, none had a bleeding tendency It is not known whether or not any of these had macroglobulinemia since ultracentrifugation of serum was not done

4. CLINICAL MANIFESTATIONS

Pain in the Bones

The most characteristic symptom of multiple myeloma is bone pain. This was present in all but eight of the ninety-seven cases in this series—92 per cent. The onset is usually gradual with fleeting, migratory pains, although occasionally it is abrupt in onset and associated with a pathologic fracture. Many patients complain of pain in several places at the same time or even of generalized bone pain As has been pointed out repeatedly, the pains of myeloma patients are most frequently localized in the lower back and in the rib cage In our patients, too, the most common sites were the back (75 per cent) and the rib cage (58 per cent). Other common painful sites were in hips and legs (42 per cent) and the shoulders and arms (33 per cent) Pain in the skull occurred in only three patients

The pain may vary from a mild soreness and tenderness over an isolated lesion to a pain so severe that the patient may, for fear of being jarred, tremble at the sight of someone approaching the bed The pain is characteristically made worse by movement and by coughing or sneezing With the frequent involvement of the vertebral column, there was often the additional torment of severe neuritic pain from compression of spinal nerve roots by the collapsed vertebrae The intensity of the pain may fluctuate widely during the course of the disease, and occasionally there may be spontaneous remissions when, for short periods, the patient is almost entirely free of pain In our series, very few of the cases duplicated the pain cycle described by Geschickter and Copeland[66] as being characteristic of the disease. The patient may become, in the last stages of the disease, a pain-wracked invalid, completely bedridden, forced to lie for unending hours in an unchanging position, requiring opiates around the clock.

behave like beta or gamma globulins. These sera usually give a strong euglobulin reaction with the sodium sulfate fractionation, but Bichel, Bing, and Harboe[26] describe one case of macroglobulinemia in which the euglobulin reaction was negative. Cases with macroglobulinemia, fever, and central nervous system degeneration (paresis, increase of globulin in the spinal fluid) have also been described.[26] The complete syndrome as described by Waldenström was not seen in any of the cases in the present series. In those of our cases which were complicated by purpura or excessive bleeding, none had simple demineralization on x-ray examination. All but two had multiple osteolytic lesions, and these two had no demonstrable lesions at all. Of five myeloma patients with generalized demineralization of the bone but no discrete lytic lesions, none had a bleeding tendency. It is not known whether or not any of these had macroglobulinemia since ultracentrifugation of serum was not done.

4. CLINICAL MANIFESTATIONS

Pain in the Bones

The most characteristic symptom of multiple myeloma is bone pain This was present in all but eight of the ninety-seven cases in this series—92 per cent. The onset is usually gradual with fleeting, migratory pains, although occasionally it is abrupt in onset and associated with a pathologic fracture. Many patients complain of pain in several places at the same time or even of generalized bone pain As has been pointed out repeatedly, the pains of myeloma patients are most frequently localized in the lower back and in the rib cage In our patients, too, the most common sites were the back (75 per cent) and the rib cage (58 per cent) Other common painful sites were in hips and legs (42 per cent) and the shoulders and arms (33 per cent) Pain in the skull occurred in only three patients

The pain may vary from a mild soreness and tenderness over an isolated lesion to a pain so severe that the patient may, for fear of being jarred, tremble at the sight of someone approaching the bed. The pain is characteristically made worse by movement and by coughing or sneezing With the frequent involvement of the vertebral column, there was often the additional torment of severe neuritic pain from compression of spinal nerve roots by the collapsed vertebrae The intensity of the pain may fluctuate widely during the course of the disease, and occasionally there may be spontaneous remissions when, for short periods, the patient is almost entirely free of pain In our series, very few of the cases duplicated the pain cycle described by Geschickter and Copeland[66] as being characteristic of the disease. The patient may become, in the last stages of the disease, a pain-wracked invalid, completely bedridden, forced to lie for unending hours in an unchanging position, requiring opiates around the clock.

The rare patients without pain are naturally the more difficult diagnostic problems. Several were among the group of cases complicated by amyloidosis. Others presented themselves with a non-hypertensive uremia of obscure etiology or ran a very short course due to fulminating myelomatosis with severe anemia or leukoerythroblastic reaction caused by extensive bone-marrow replacement

Pathologic Fractures

In addition to bone pain, fifty-nine of ninety-seven patients (62 per cent) had one or more fractured bones (fig. 7). By far the most

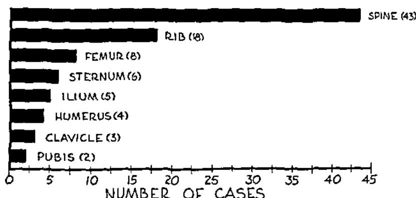


Fig 7 —Incidence of pathologic fracture in multiple myeloma

common were compression fractures of the spine These occurred in 48 per cent of the cases, and in many patients fractures were limited to the spine (figs 8 and 9) The compressed vertebral bodies were found most frequently in the lower thoracic and upper lumbar region The next most frequent site of pathologic fracture was in the ribs (19 per cent) Fractures of bones other than vertebrae or ribs occurred in twenty-eight patients (29 per cent) These included the femur, (eight), sternum (six), ilium (five), humerus (four), clavicle (three), and pubis (two)

The fact that six patients sustained a partial or complete transverse fracture of the body of the sternum is worthy of more than passing comment (fig 10). A fracture of the sternum with its resultant deleterious effect on the mechanics of respiration is an extremely serious event Many of these patients have limited pulmonary function due to chronic bronchitis and emphysema associated with recurrent bronchopneumonic episodes. The onset of paradoxic respiratory

motion of the chest wall following a sternal fracture may so seriously impair ventilatory capacity as to cause death. One patient at autopsy was found to have considerable displacement of the heart and a 5 to

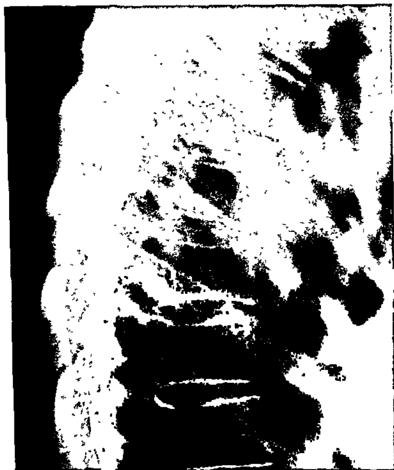


FIG 8 —Collapse of dorsal vertebral body infiltrated by myeloma

7 cm recession of the entire anterior rib cage secondary to a sharply angulated fracture of the sternum at the level of the third rib The relationship of sternal marrow puncture to such fractures is unclear, but it may be wiser to use the iliac crest as the site of election for marrow puncture if repeated studies are to be made

Usually fractures in multiple myeloma patients heal rapidly

(fig. 28) There is a remarkably good callus formation which some authors assert may be related to the hypercalcemia frequently present in multiple myeloma Due to multiple partial or complete fractures deformation of the skeleton occurs very frequently. Most commonly encountered is malformation of the thorax The spine is usually shortened, the rib cages approach the rim of the pelvis, and severe kyphosis or scoliosis with disappearance of the lumbar lordosis are



Fig 9 —(a) Beginning destruction of cervical vertebral body. (b) Complete collapse of cervical vertebral body

found The gait first becomes difficult and ultimately the patient is immobilized in bed. Finally the condition becomes so desperate that the patient and his family welcome a terminal pneumonia which at last can put an end to useless suffering.

Tumor Formation

In twenty-four of our patients, plasmocytomas of the bones became so large that they were palpable. These tumors were found in the ribs (seven), skull (five), ilium (three), clavicle (three), sternum (two), and humerus (one) (fig 11a,b). These figures coincide well with the data in the literature. Léger et al.[102a] also found that the ribs, skull, femur, humerus, sternum, and sacrum are the most frequent sites of



FIG 10 —Complete transverse fracture of sternum destroyed by myeloma.

palpable tumors. In one patient, a walnut-sized tumor mass, composed entirely of sheets of plasma cells, extended from a large area of bone destruction in the maxilla This mass was found on the inner aspect of the gingiva, medial to the left upper first molar, and represented the patient's only complaint on admission (fig. 12a,b). Further

study revealed that this patient had massive involvement of the entire skeleton consisting of punched out areas of destruction and that the urine was positive for Bence Jones protein.



FIG 11*a* —Autopsy specimen of humerus showing the tumor formation, complete disruption of cortex, and replacement of the medullary cavity by gelatinous myeloma tissue

Palpable tumor masses varied in size from that of a pea to that of a grapefruit They were generally firm, bony, or rubbery in consistency, depending on whether or not the cortex of the bone had been eroded, and they were usually quite tender. Palpable plasmocytomas of the skull were usually soft. Large palpable lesions at times seemed almost fluctuant and in two patients tumors appearing just beneath the skin

were warm, tender, and red, giving the appearance of suppurative lesions. Needle aspirations in these two cases yielded solid masses of myeloma cells Sometimes the shell of bone which has remained is so



FIG 11*b* —Roentgenogram of lesion shown in figure 11*a*, during life, showing marked destruction, demineralization, and "soap bubble" effect

thin that it can be indented like parchment A definite systolic bruit was audible over a huge tumor mass arising from the wing of the left ilium The bruit was only discovered a few months after a biopsy of this tumor had been performed It is, therefore, possible that the bruit did not arise in the original plasmocytoma; after biopsy of vascular tumors and parenchymatous organs, arteriovenous aneurysms may develop if a suturing needle perforates an artery and a contiguous

FIG 12*a* —Plasmocytoma of maxilla in a patient with widespread multiple myeloma

FIG 12*b* —Microscopic section of tumor shown in figure 12*a*

vein. A rapidly growing tumor of the humerus caused grotesque deformity of one patient's arm and was associated with a pathologic fracture. In this case the roentgen appearance gave an unusual soap bubble effect (fig. 11a,b). By involvement of contiguous organs such as ureters, lungs, nerve roots, or the spinal cord itself, these myelomatous tumors may occasionally produce localizing symptoms and signs in addition to pain.

In five cases soft tumors were palpable overlying large destructive lesions in the skull Occasionally these tumors are pulsatile, probably due to the transmission of the pulsation of the intracranial contents [44] Three of these nodules displayed a remarkable sensitivity to local x-ray therapy, virtually melting away and leaving palpable, irregular defects in the outer table of the cranium. Saltzman and Borgstrom[160] reported a case of skull and chest tumors disappearing concurrently with urethane therapy Rubinstein[153] reported disappearance of skull tumors with antimony (neostibosan), but this has not been confirmed

In their comprehensive article on multiple myeloma written over twenty years ago, Geschickter and Copeland[66] reported that tumors were palpable in 90 per cent of the cases they reviewed The considerable discrepancy between that figure and the relatively low figure (25 per cent) in this series, may be attributed to the wider use of diagnostic sternal marrow puncture at the present time. This technic was not generally in use before 1930 and therefore early and less flagrant cases of myeloma without tumor formation might easily have been overlooked.

Pulmonary Involvement

Because of the marked morphologic and biochemical changes which occur in myeloma, symptoms referable to any system of the body may be present. Since the disease occurs primarily in older people, it is frequently difficult to determine whether a given symptom is directly related to multiple myeloma or is caused by an independent and unrelated disease In this series of ninety-seven cases, 50 per cent of the patients suffered from symptoms referable to the lungs There were twenty-four patients who had at least one episode of pneumonia during their illness, exclusive of terminal pneumonia Thirteen patients had recurrent pneumonia and several of these had five or six such episodes within a two year period One such patient consulted many physicians for the relief of recurrent episodes of high fever,

cough, and purulent sputum over a three year period When severe and crippling back pain began, it was felt that the patient had a carcinoma of the bronchus with metastases to the spine. The true nature of the process was revealed only when a sternal puncture showed that the marrow contained large numbers of myeloma cells.

Recurrent pneumonias occurred most frequently in those patients with highly elevated serum globulin Geschickter and Copeland[68] remarked on the frequency of a diffuse, persistent bronchitis of the mucopurulent variety seen so often in patients with multiple myeloma. They felt that the debilitated state, the hypostatic changes dependent on long periods of bed rest, and the restricted alveolar ventilation brought about by painful respiration were contributory factors Kyphosis of the dorsal spine, already mentioned above, with resultant pulmonary emphysema constitutes another factor impairing ventilatory capacity and predisposing to pneumonia. A possible additional factor may be a sluggish pulmonary circulation related to high serum globulin, increased blood viscosity, and the tendency to rouleau formation of the red cells Measurements of blood viscosity have been made by many observers[4, 117, 201] and the viscosity values in some cases of multiple myeloma have surpassed all hitherto observed levels. Finally, the antibody levels in the serum of myeloma patients are often markedly decreased (p. 73) This combination of abnormal conditions is ideal for the production of small pulmonary infarctions, which then may become secondarily infected and simulate the picture of recurrent bronchopneumonic episodes. All this might explain the repeated "pneumonias" which often occur in a myeloma patient even before he becomes bedridden or develops spine and rib lesions It also sheds light on long drawn-out febrile or subfebrile periods which occasionally precede the discovery of the presence of multiple myeloma. An analogous situation of intravascular thrombosis associated with excessive viscosity of the blood may conceivably have existed in the case of myeloma reported by Wintrobe and Buell,[212] where a fully developed Raynaud's syndrome occurred, together with central retinal vein thrombosis. Signs of peripheral vascular occlusion are especially frequent in patients with cryoglobulinemia.

The roentgen appearance of intrathoracic neoplasms may be simulated by myelomatous tumors arising in the thoracic cage. We have repeatedly encountered myeloma patients in whom the chest x-rays revealed the presence of multiple subpleural tumors arising in



FIG 13a—Myelomatous involvement of several ribs simulating metastatic carcinoma of the lungs

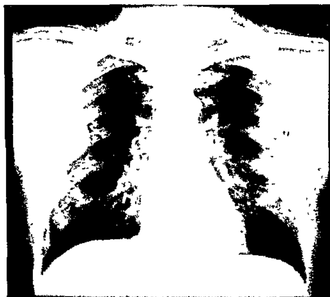


FIG 13b—Extension of myeloma of rib subpleurally, producing the picture of a pleural scallop seen in metastatic disease

the ribs, resembling the picture of metastatic carcinoma of the lungs (fig 13a,b) In one patient with myeloma and recurrent pneumonia, roentgen examination revealed a shadow which gave the impression of a mediastinal mass. At autopsy this was found to be a myelomatous tumor arising from the left posterior chest wall and involving the mediastinal structures and the left lower lobe of the lung. Serofibrinous pleurisy occasionally occurs in multiple myeloma but can usually be explained by the presence of subpleural myeloma nodules or as a sequela to fractures of the ribs.

Neurologic Symptoms and Signs

Neurologic involvement, which is common in multiple myeloma, may be of two types. Most often, symptoms develop from direct involvement of nervous tissue, either by extension of myelomatous tissue from neighboring bones or by compression of nervous tissue by collapsed vertebrae. Not infrequently, however, the symptoms are those of a peripheral neuritis where no direct involvement of nerves or nerve roots can be demonstrated.

Shenkin, Horn, and Grant[170] studied fifty-four lesions of the spine which produced cord compressions and found eight of these to be caused by myeloma Among the noninflammatory lesions of the spine producing cord compression only metastatic carcinoma occurs more frequently than myeloma. Davison and Balser[46] in studying twelve cases of multiple myeloma with neurologic complications came to the conclusion that neurologic signs in the disease could always be explained on the basis of compression of the cord or its vessels This conclusion however is in contradiction to reports, by Nonne,[120] Kreuzer,[95] Scheinker,[163] and more recently Kurnick and Yohalem,[100] of cases where neurologic symptoms developed in the absence of direct nervous tissue involvement. Scheinker described a type of perineuritis, which may occasionally be the cause of neuritic pains in myeloma. Only rarely does myeloma of the skull cause cerebral compression. Occasionally, invasion of brain tissue,[195] coma and proptosis of an eye,[210] cranial nerve palsy,[7,32] or thrombosis of an intracranial sinus or central retinal artery[198] may be caused by such cranial tumors

Forty per cent of the ninety-seven cases in this series developed symptoms referable to the nervous system. Spinal cord compression occurred in seven patients. Four of these had cord bladders associated

with paraplegia. One developed a cord bladder without paraplegia and another had weakness of the right leg with clonus but no other signs. All seven had roentgen evidence of one or more compression fractures of the spine Two of these patients experienced considerable relief and return of function after decompression of the cord and laminectomy. The tissue pressing on the cord in each instance was found to be a plasma cell myeloma. Although cord compression often occurs as a complication of multiple myeloma in patients who are riddled with the disease, it is also observed frequently in cases of plasmocytoma where clear cut evidence of generalized myelomatous involvement is lacking (p. 100). Several such cases with negative bone marrow have been reported recently [43]

The following patient suffered from a plasmocytoma of the spine leading to a transverse lesion of the cord As far as could be ascertained, the rest of the skeleton was not involved

J W, #622431, a 61 year old white male with high thoracic back pain for one year and weakness of the legs for one month, was unable to walk at the time of his admission to the hospital He had no bladder or rectal symptoms Examination revealed bilateral Babinski signs and marked weakness and hyperreflexia of the lower extremities A sensory level was found below D 6 There was point tenderness over D 5 and D 6 Lumbar puncture showed a complete block and a myelogram demonstrated an irregularly capped defect at D 6 X-ray of the spine revealed a destructive lesion in the body, pedicles and spinous process of D 6, and demineralization of D 5 The remainder of the skeleton was normal, except for an ovoid area of increased lucency in the [illegible] 25) There [illegible] evated, and [illegible]

Laminectomy at D 5 to D 7 revealed a large, extradural, friable, extremely vascular tumor extending through the laminal arches into the epidural space [illegible]

the wound had healed Because of the bizarre x-ray appearance of the lesion in the ilium with a sclerotic outer rim, it was biopsied and reported to be a xanthoma of bone, not a myeloma

Follow-up examination one year later showed the patient to be well with only minimal residual paresthesias of the feet and no bone pain. No further progression or dissemination of the disease was noted at the time

Fifteen patients showed clinical evidence of involvement of spinal cord roots or of peripheral nerves Five of these had simple root pain

with band-like radiation around the chest or abdomen or down the leg Four cases developed a "glove and stocking" type of peripheral neuritis. The others demonstrated a variety of neurologic changes such as hypesthesias, paresthesias, foot drop, or loss of proprioceptive sensation None of this group of patients had vertebral collapse. These neurologic signs may well have been due—at least in some cases—to the perineuritis mentioned above.[100,163] Another type of abnormality was noted in three cases in which the sole neurologic disturbance was unilateral ulnar nerve involvement. In one of these cases the ulnar nerve was felt to be definitely thickened and indurated.

One patient with myelomatous involvement of the cervical spine (fig. 9a,b) developed weakness and atrophy of the muscles of the shoulder girdle, while another had weakness of the right arm and a right Horner's syndrome. Several patients have shown striking atrophy of the interosseous muscles and the musculature of the arms without other evidence of neurologic involvement.

Cranial nerve palsy occurred in three of the patients One developed an isolated left abducens nerve paralysis with no roentgen evidence of bone destruction in the skull A second demonstrated a right ophthalmoplegia In this case destruction of the floor and posterior wall of the sella turcica was seen in skull x-rays and at a postmortem a large myelomatous tumor mass was found to have displaced the pituitary forward and to have eroded the posterior portion of the body of the sphenoid In the third case there was paralysis of all the cranial nerves from VII to XII on one side caused by a large destructive lesion at the base of the skull The diagnosis in the last case was established by biopsy of a bluish mass which proved to be a plasmocytoma presenting through the external auditory canal. Marked but temporary remission of neurologic signs in these latter two cases followed radiotherapy.

Other neurologic disturbances which were encountered included a hemiplegia, repeated convulsive seizures, herpes zoster, and finally a nonspecific type of degenerative disease of the spinal cord. This condition has been reported previously by Dutch authors.[106]

Psychotic episodes unrelated to terminal events developed in eleven patients. Two of these were paranoid reactions, while the others resembled toxic psychoses characterized by confusion and disorientation Postmortem examination of the brain was carried out in seven of the patients in this group. One case revealed extensive involvement

of the skull with erosion of the inner table, but no abnormality of the underlying brain. In the other six cases, no myelomatous involvement of the brain was present. Davison and Balser[46] reported a case of myeloma with a psychosis which they felt could possibly have been attributed to compression of cerebral vessels by myeloma nodules in the cerebral dura.

Renal and Urinary Tract Involvement

The severe renal impairment, which occurs not infrequently, in multiple myeloma and which has as its pathologic equivalent the "myeloma kidney",[121] has been the subject of much discussion in the literature The pathologic lesion in the kidney was first described by von Decastello in 1908 [47] Geschickter and Copeland[66] found that 86 per cent of the cases they studied showed evidence of "nephritis" at autopsy, and that 61 per cent were associated with Bence Jones proteinuria Bence Jones protein may be found in myeloma kidneys in three different forms 1) as large hyaline drops in the lumen of the tubules and in the tubular epithelium; 2) as crystalline material in the tubular lumen and in the tubular cells; 3) as amorphous precipitates in the form of casts

The modern physicochemists have designated the formation of large drops in colloid sols as coacervation This coacervation is often followed either by crystallization or by precipitation of the colloid This explains the occasional occurrence of crystallization of protein, probably Bence Jones protein, in tubules and tubular walls. The Bence Jones casts must then be the result of precipitation of these coacervates

Oliver,[137] using his vividly clear nephron dissection technic, has emphasized that cast formation in the myeloma kidney is more extensive than in any other renal disease He has found that, whereas casts in other renal diseases are usually limited to the distal convoluted tubules and the collecting tubules, the cast formation in the myeloma kidney may extend as high as the proximal convoluted tubule The entire nephron is often filled solidly with Bence Jones protein casts, resulting in extreme distension, deformity, and atrophy of the renal architecture (fig 14) From a morphologic point of view, Oliver's preparations leave little doubt that severe renal damage can result from the cast blockade in these kidneys. Ehrich[54] introduced the term "nephrohydrosis" (internal or intrarenal hydronephrosis) to describe

with band-like radiation around the chest or abdomen or down the leg Four cases developed a "glove and stocking" type of peripheral neuritis The others demonstrated a variety of neurologic changes such as hypesthesias, paresthesias, foot drop, or loss of proprioceptive sensation None of this group of patients had vertebral collapse. These neurologic signs may well have been due—at least in some cases—to the perineuritis mentioned above [100,163] Another type of abnormality was noted in three cases in which the sole neurologic disturbance was unilateral ulnar nerve involvement. In one of these cases the ulnar nerve was felt to be definitely thickened and indurated

One patient with myelomatous involvement of the cervical spine (fig 9a,b) developed weakness and atrophy of the muscles of the shoulder girdle, while another had weakness of the right arm and a right Horner's syndrome. Several patients have shown striking atrophy of the interosseous muscles and the musculature of the arms without other evidence of neurologic involvement.

Cranial nerve palsy occurred in three of the patients. One developed an isolated left abducens nerve paralysis with no roentgen evidence of bone destruction in the skull. A second demonstrated a right ophthalmoplegia. In this case destruction of the floor and posterior wall of the sella turcica was seen in skull x-rays and at a postmortem a large myelomatous tumor mass was found to have displaced the pituitary forward and to have eroded the posterior portion of the body of the sphenoid In the third case there was paralysis of all the cranial nerves from VII to XII on one side caused by a large destructive lesion at the base of the skull. The diagnosis in the last case was established by biopsy of a bluish mass which proved to be a plasmocytoma presenting through the external auditory canal. Marked but temporary remission of neurologic signs in these latter two cases followed radiotherapy

Other neurologic disturbances which were encountered included a hemiplegia, repeated convulsive seizures, herpes zoster, and finally a nonspecific type of degenerative disease of the spinal cord. This condition has been reported previously by Dutch authors.[106]

Psychotic episodes unrelated to terminal events developed in eleven patients. Two of these were paranoid reactions, while the others resembled toxic psychoses characterized by confusion and disorientation Postmortem examination of the brain was carried out in seven of the patients in this group. One case revealed extensive involvement

of the skull with erosion of the inner table, but no abnormality of the underlying brain. In the other six cases, no myelomatous involvement of the brain was present. Davison and Balser[48] reported a case of myeloma with a psychosis which they felt could possibly have been attributed to compression of cerebral vessels by myeloma nodules in the cerebral dura.

Renal and Urinary Tract Involvement

The severe renal impairment, which occurs not infrequently, in multiple myeloma and which has as its pathologic equivalent the "myeloma kidney",[131] has been the subject of much discussion in the literature. The pathologic lesion in the kidney was first described by von Decastello in 1908.[47] Geschickter and Copeland[88] found that 86 per cent of the cases they studied showed evidence of "nephritis" at autopsy, and that 61 per cent were associated with Bence Jones proteinuria. Bence Jones protein may be found in myeloma kidneys in three different forms: 1) as large hyaline drops in the lumen of the tubules and in the tubular epithelium, 2) as crystalline material in the tubular lumen and in the tubular cells, 3) as amorphous precipitates in the form of casts.

The modern physicochemists have designated the formation of large drops in colloid sols as coacervation. This coacervation is often followed either by crystallization or by precipitation of the colloid. This explains the occasional occurrence of crystallization of protein, probably Bence Jones protein, in tubules and tubular walls. The Bence Jones casts must then be the result of precipitation of these coacervates.

Oliver,[137] using his vividly clear nephron dissection technic, has emphasized that cast formation in the myeloma kidney is more extensive than in any other renal disease. He has found that, whereas casts in other renal diseases are usually limited to the distal convoluted tubules and the collecting tubules, the cast formation in the myeloma kidney may extend as high as the proximal convoluted tubule. The entire nephron is often filled solidly with Bence Jones protein casts, resulting in extreme distension, deformity, and atrophy of the renal architecture (fig. 14). From a morphologic point of view, Oliver's preparations leave little doubt that severe renal damage can result from the cast blockade in these kidneys. Ehrich[54] introduced the term "nephrohydrosis" (internal or intrarenal hydronephrosis) to describe

this type of renal damage. The casts are not only more extensive but also much larger than the ones occurring in chronic glomerulonephritis. Often, the casts in myeloma kidneys consist of concentric layers Each layer may be surrounded by giant cells (fig. 15). This remarkable picture apparently indicates that these successive layers were deposited at different intervals. Bell[20] feels that the renal damage which is so common in multiple myeloma is caused by these Bence



Fig 14 —Microphotograph of myeloma kidney showing extensive cast formation One cast appears lamellated and has a calcified center.

Jones protein casts. Acting as foreign bodies, these casts lead to obstruction and tubular atrophy In the initial stages, the glomeruli are intact In the long run, however, the obstruction of the tubular flow leads to atrophy of the glomeruli and contraction of renal parenchyma and ultimately to severe renal insufficiency. Bell[20] could find, in the literature, only one case of multiple myeloma with a high degree of renal insufficiency and a negative reaction for Bence Jones protein in the urine

Apitz[8] is of the opinion that the large hyaline protein drops which are so frequently seen in the tubular cells of myeloma kidneys repre-

sent Bence Jones protein which is being excreted by the tubules It seems equally plausible, as has been emphasized by Oliver, that these droplets could consist of protein which has been reabsorbed from the tubular lumen into the tubular epithelial cells The toxic effect of this reabsorbed Bence Jones protein may well lead to additional tubular injury *The latter, when superimposed upon the damage resulting* from the blockage of tubules by Bence Jones protein, can cause severe

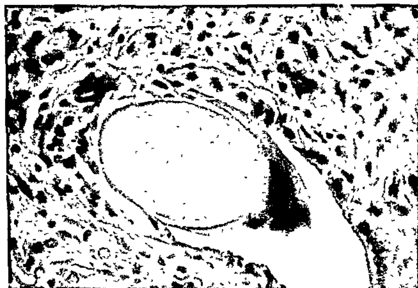


FIG 15—High power view of myeloma kidney with tubular cast surrounded by a foreign body giant cell.

renal insufficiency Blackman[31a] is of the opinion that, whereas albumin in the urine does not, of itself, damage the kidney, Bence Jones protein and beta globulins are harmful It is difficult to determine which of the two—the presence of these large protein globules in the tubular cells or the formation of the giant casts—is the more important factor in impairing the function of the myeloma kidney Apitz, however, particularly incriminates the protein globules in the renal cells He found, at autopsy of myeloma cases with Bence Jones proteinuria of short duration, that though cast formation was still negligible, the tubular epithelial cells were nevertheless already overfilled with hyaline droplets

Recent physiologic studies suggest that the primary mechanism of

the renal insufficiency in myeloma may not be the simple one offered by Bell Homer Smith[173] has exhaustively reviewed the problem of renal disease associated with obstructive cast formation, irrespective

TABLE 3 —*Studies of Renal Function in Five Myeloma Patients**

	Inulin clearance cc /min	PAH clearance cc /min	Filtration fraction $\frac{C\ in}{C\ PAH} \times 100$	Tm PAH mg /min	C in/ Tm PAH	Effective renal blood flow cc /min	Blood urea nitrogen (mg %)
Normal	120	600	20	80	1 5	1000	15
M S	53 8	280	19 2	40 2	1 34	455	16
B K	28 4	143	19 9	26 7	1 06	246	24
W P	99 6	506	19 7	84 1	1 18	778	20
M B	1 96	1 89	—	0 01	—	—	130
L H	4 25	8 12	—	1 45	—	—	107

* Courtesy of Dr Jonas Sirota

of whether these casts consist of hemoglobin, myoglobin or precipitated protein He seriously doubts that in such conditions, collected under the unfortunate label of "lower nephron nephrosis", the entire picture is explained by the tubular occlusive phenomena seen on pathologic section Armstrong[11] studied fifteen cases of proven myeloma, none of which had any severe degree of renal insufficiency as determined by routine clinical testing Glomerular filtration rate was found to be impaired to an equal or greater extent than the tubular excretory capacity in eleven of the fifteen patients studied Where the primary fault is tubular obstruction, one would expect tubular function to be depressed at least as much as, if not more than, the glomerular filtration rate Such a pattern was found by Corcoran and Page[40] in induced hemoglobin nephrosis in dehydrated dogs and is the reverse of the situation found in the myeloma patients studied by Armstrong On the other hand, in a group of nine patients studied by Goldman, Adams, and Luchsinger,[88a] there was a parallel reduction in all three modalities of renal function This, they suggested, resulted from the destruction of whole nephron units

Five patients in this series, two of whom were in severe uremia, were studied in this manner by Dr Jonas Sirota (table 3). In the three patients with relatively normal renal function, the filtration rate, renal plasma flow, and tubular secretory maximum were all depressed.

However, the decrease in the ratio C in/Tm PAH indicates, as was also noted by Armstrong, that there was relatively greater sparing of tubular function than of glomerular function or plasma flow. The two patients with signs of far advanced clinical uremia had a blood urea nitrogen of 107 and 130 mg. per cent respectively These two cases demonstrated such marked depression of all three modalities that no conclusions could be drawn. Although the morphologic evidence is extremely impressive and would seem to indicate that the myeloma kidney suffers from "stopped-up pipes,"[137] physiologic data obtained during life would tend to implicate an additional lesion to explain the renal insufficiency caused by the myeloma kidney

The myeloma kidney, while it does cause severe uremia, does not lead to hypertension The incidence of hypertension in Bell's series was 26 per cent, a figure which he felt corresponded closely to the coincidence of hypertension in elderly patients, and which could not be attributed to multiple myeloma unless essential hypertension was excluded Thirteen of the forty-one autopsied cases in this series showed the pathologic picture of the myeloma kidney on microscopic section Nine of these cases died with severe uremia, only one of these had a blood pressure with systolic levels above 150 mm Hg and diastolic levels above 90 mm Of the entire series of forty-one autopsied cases, only six had blood pressures in the hypertensive range (15 per cent) (fig 16) Thus, our series would confirm the impression that the uremia caused by the myeloma kidney is nonhypertensive (fig 17) This becomes a valuable diagnostic point in the approach to any uremia without hypertension The following is a case history* describing just such a patient, misdiagnosed as chronic glomerulonephritis

M B, #601321, a 45 year old white salesman, was admitted for the first time to the private service, complaining of marked weakness, fatigue, nausea, diarrhea, and pain in the right lower quadrant of three months duration The patient reported an ammoniacal taste in his mouth and had lost 20 pounds Examination revealed a chronically ill male with uremic odor to the breath

erythrocyte sedimentation rate 95 mm per hour. Cystoscopy and pyelography were negative After several transfusions the patient was discharged unimproved with the diagnosis of chronic glomerulonephritis

*This case history has already appeared elsewhere [178]

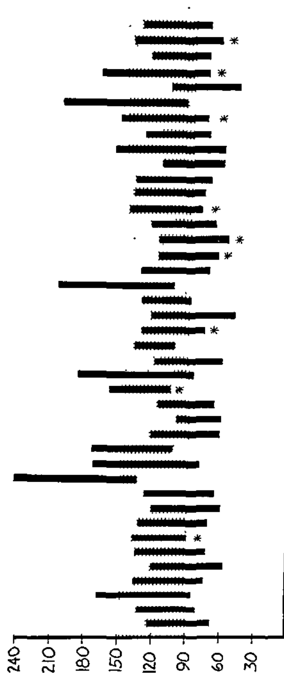


Fig. 16.—Blood pressure range in the forty-one autopsied patients with multiple myeloma

differential except for the presence of 4 per cent plasma cells The blood urea

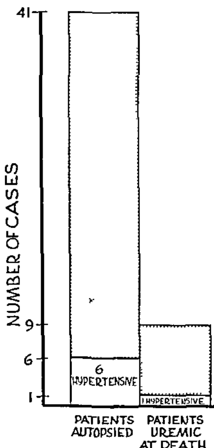


Fig 17.—The incidence of hypertension among the uremic patients in the forty-one autopsied cases of myeloma

nitrogen was 225 mg per cent, creatinine 18 7 mg per cent, calcium 7 8 mg per cent, phosphorus 8 3 mg per cent, CO_2 22 4 vol per cent, serum albumin 4 0 Gm per cent, globulin, 2 4 Gm per cent The electrophoretic pattern revealed only minor anomalies The urine showed 3 plus albuminuria Because of the obscure etiology of this nonhypertensive uremia and the presence of plasma cells in the peripheral blood, a careful Jacobson test for Bence Jones proteinuria was carried out and found to be positive A roentgenologic skeletal

survey failed to reveal any bone lesion compatible with the diagnosis of multiple myeloma. Sternal aspiration, however, showed that the marrow contained large numbers of immature plasma cells, with many binucleate forms The patient's course was steadily downhill and he died within a short time Postmortem examination revealed multiple myeloma, myeloma kidneys, and paramyloidosis of the heart, gastrointestinal tract, periadrenal fat, and spleen

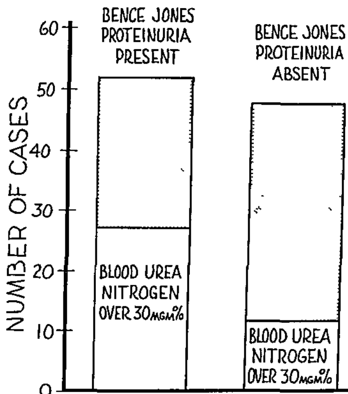


FIG 18 —The relationship between elevation of the blood urea nitrogen and Bence Jones proteinuria Elevation of the blood urea nitrogen occurs more than twice as frequently in patients with Bence Jones proteinuria

A definite relationship seems to exist between the presence of Bence Jones proteinuria and an increased incidence of renal insufficiency. All thirteen of the patients with myeloma kidneys at autopsy had Bence Jones protein in the urine during life. There were fifteen patients who developed elevation of the blood urea nitrogen to 60 mg per cent or higher, every one of whom had Bence Jones protein in the urine. Thus, in the differential diagnosis of moderately severe renal insufficiency, the absence of Bence Jones proteinuria would make multiple myeloma an unlikely etiologic possibility. Of those patients

who showed a positive test for Bence Jones protein in the urine, 55 per cent had a blood urea nitrogen of over 30 mg per cent, while only 24 per cent of those with a negative Bence Jones reaction demonstrated a comparable elevation of the blood urea nitrogen (fig 18) There was an approximately equal number of patients in this group, since 49 per cent of the patients in this series had Bence Jones proteinuria

Examination of the urine of the 97 cases in this series revealed the presence of albuminuria at one time or another in 90 per cent of the cases; 50 per cent had 2 plus albuminuria or more; 80 per cent showed white blood cells on microscopic examination of the urinary sediment, 45 per cent had red cells and 19 per cent had casts Only seven cases in the entire series had normal urinary findings at all times The forty-eight cases who had Bence Jones proteinuria, with an occasional exception, also had albuminuria However, forty-two cases had albuminuria without Bence Jones proteinuria Fishberg concentration tests were run on sixty-three patients, half of whom could not concentrate the urine above a specific gravity of 1 018, of this group with moderate impairment of concentrating ability, 75 per cent had Bence Jones proteinuria Phenolsulphonephthalein tests were run on sixty-five patients, one half of these patients could not excrete 60 per cent of the dye in two hours and one third could not excrete 40 per cent of the dye in two hours The impairment of excretion of phenolsulphonephthalein is an early sign of renal failure in Bence Jones proteinuria

Lymphadenopathy and Hepatosplenomegaly

Extraskeletal myelomatous involvement has been reported frequently in the literature [35,37,66,82,111 142] Churg and Gordon[35 37] demonstrated that there is a surprisingly high incidence of myelomatous infiltration of the extraosseous hematopoietic system in multiple myeloma In thirty consecutive autopsied cases which they studied at the Mount Sinai Hospital, they found 73 per cent to have either diffuse or nodular infiltration of the liver, spleen, and lymph nodes by myeloma cells In our ninety-seven cases, palpable hepatomegaly was present in thirty-seven patients (40 per cent) and hepatosplenomegaly in twenty-two patients (23 per cent) The liver was almost always smooth, firm, and non-tender, although occasionally slight tenderness was elicited Enlargement, as detected by physical examination, ranged up to 10 cm below the right costal margin The splenic

survey failed to reveal any bone lesion compatible with the diagnosis of multiple myeloma Sternal aspiration, however, showed that the marrow contained large numbers of immature plasma cells, with many binucleate forms The patient's course was steadily downhill and he died within a short time Postmortem examination revealed multiple myeloma, myeloma kidneys, and paramyloidosis of the heart, gastrointestinal tract, periadrenal fat, and spleen

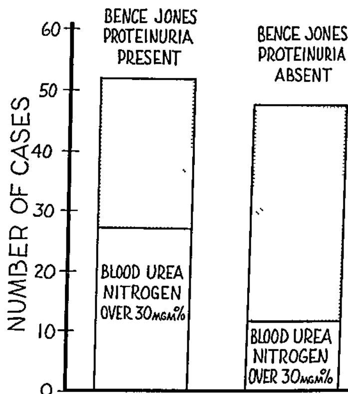


FIG 18 —The relationship between elevation of the blood urea nitrogen and Bence Jones proteinuria Elevation of the blood urea nitrogen occurs more than twice as frequently in patients with Bence Jones proteinuria

A definite relationship seems to exist between the presence of Bence Jones proteinuria and an increased incidence of renal insufficiency. All thirteen of the patients with myeloma kidneys at autopsy had Bence Jones protein in the urine during life. There were fifteen patients who developed elevation of the blood urea nitrogen to 60 mg. per cent or higher, every one of whom had Bence Jones protein in the urine. Thus, in the differential diagnosis of moderately severe renal insufficiency, the absence of Bence Jones proteinuria would make multiple myeloma an unlikely etiologic possibility. Of those patients

who showed a positive test for Bence Jones protein in the urine, 55 per cent had a blood urea nitrogen of over 30 mg per cent, while only *24 per cent of those with a negative Bence Jones reaction demonstrated* a comparable elevation of the blood urea nitrogen (fig 18) There was an approximately equal number of patients in this group, since 49 per cent of the patients in this series had Bence Jones proteinuria

Examination of the urine of the 97 cases in this series revealed the presence of albuminuria at one time or another in 90 per cent of the cases, 50 per cent had 2 plus albuminuria or more, 80 per cent showed white blood cells on microscopic examination of the urinary sediment, 45 per cent had red cells and 19 per cent had casts Only seven cases in the entire series had normal urinary findings at all times The forty-eight cases who had Bence Jones proteinuria, with an occasional exception, also had albuminuria However, forty-two cases had albuminuria without Bence Jones proteinuria Fishberg concentration tests were run on sixty-three patients, half of whom could not concentrate the urine above a specific gravity of 1 018, of this group with moderate impairment of concentrating ability, 75 per cent had Bence Jones proteinuria Phenolsulphonephthalein tests were run on sixty-five patients, one half of these patients could not excrete 60 per cent of the dye in two hours and one third could not excrete 40 per cent of the dye in two hours The impairment of excretion of phenolsulphonephthalein is an early sign of renal failure in Bence Jones proteinuria

Lymphadenopathy and Hepatosplenomegaly

Extraskeletal myelomatous involvement has been reported frequently in the literature[26,27,66,82,111,112] Churg and Gordon[26,87] demonstrated that there is a surprisingly high incidence of myelomatous infiltration of the extraosseous hematopoietic system in multiple myeloma In thirty consecutive autopsied cases which they studied at the Mount Sinai Hospital, they found 73 per cent to have either diffuse or nodular infiltration of the liver, spleen, and lymph nodes by myeloma cells In our ninety-seven cases, palpable hepatomegaly was present in thirty-seven patients (40 per cent) and hepatosplenomegaly in twenty-two patients (23 per cent). The liver was almost always smooth, firm, and non-tender, although occasionally slight tenderness was elicited Enlargement, as detected by physical examination, ranged up to 10 cm. below the right costal margin The splenic

enlargement was usually only moderate, ranging up to 3 cm below the left costal margin, although in two cases the spleen tip extended down to the iliac crest. Clinically, it is unusual to find more than moderate enlargement of the lymph nodes, but in two cases the lymphadenopathy was striking. One patient with paramyloidosis was found, at postmortem examination, to have nodes which were markedly enlarged and virtually replaced by amyloid. This case will be presented in detail in the section on paramyloidosis. The history of a patient with lymphadenopathy, hepatosplenomegaly, and plasma cell leukemia follows:

[illegible] months [illegible]

admission, the temperature was 100.4 F and the blood pressure 120/54. There was marked lymph node enlargement varying from 1 to 3 cm in diameter. These nodes were firm, rubbery, non-tender, and in some areas matted together The liver was enlarged 4 cm below the right costal margin and the spleen was felt 2 cm below the left costal margin.

There was a moderate anemia of 12 Gm per cent of hemoglobin and a leukocytosis of 38,000 per cu mm of which 51 per cent were immature plasma cells Bone marrow aspiration revealed 10 per cent myeloma cells The erythrocyte sedimentation rate was 119 mm. per hour The serum albumin was 0 9 Gm per cent, the globulin 8 9 Gm per cent The blood nitrogen was 28 mg per cent and serum uric acid 8 9 mg per cent Bence Jones protein was found in the urine X-ray examination revealed marked scoliosis of the dorsal spine with lateral wedging of the dorsal vertebrae

The patient's hospital course was characterized by progressive anemia and by recurrent episodes of bronchopneumonia. The patient failed to respond to transfusions or to stilbamidine The peripheral blood picture changed terminally, with the white cell count falling to 8000 per cu mm. with a relatively normal differential, while the plasma cells dropped to only 1 per cent The patient died during the fifth week of hospitalization of bronchopneumonia and pulmonary edema.

Postmortem examination showed multiple myeloma with plasma cell leukemia and infiltration of lymph nodes, bone marrow, liver, spleen (fig 19), and kidneys Enlarged nodes were found in the cervical, axillary, inguinal, hilar, periaortic, and periportal areas The bones showed softening of the trabecular structure

Liver function tests were performed in many of the patients. The cephalin flocculation was 3 or 4 plus in 19 per cent of the sixty-eight cases tested. In only five cases was the thymol turbidity test definitely positive. Twelve of the thirteen patients with positive cephalin flocculation tests had elevated serum globulin levels and all had serum albumin levels below 4 Gm. per cent. Nine of the positive reactions occurred in patients with hepatomegaly. In about 20 per cent of the

cases some degree of liver dysfunction could be demonstrated by the use of the hippuric acid and cinnamic acid tests, the bromsulphalein test, the galactose tolerance test, and prothrombin time.

Two of the cases with visceral involvement are of unusual interest from the point of view of the biogenesis of multiple myeloma and its relationship to reticulum cell sarcoma Both of these cases were reported to have reticulum cell sarcoma by lymph node biopsy during

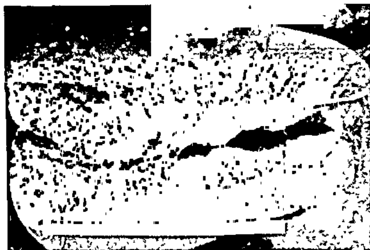


FIG 19 —Massive myelomatous infiltration of spleen

life. At autopsy, however, they were found to have a remarkable infiltration of the viscera by wildly growing, invasive cells, which resembled reticulum cells in some areas and mature myeloma cells in other areas It is interesting to speculate whether two separate disease entities occurred coincidentally in these two patients, or whether these cases may be taken as additional evidence for the reticuloendothelial origin of the myeloma process (p 10)

H C, #599016, a 61 year old male, was admitted to the hospital complaining of pain in the left hip and groin of nine months duration Seven months previously, he had been seen at another hospital, where a large destructive lesion in the wing of the left ilium was discovered and biopsied No tumor was found, the tissue section showing only "hemorrhage, inflammatory response and new bone formation " One month before admission he noted a rapidly growing mass in the region of the biopsy

Physical examination revealed a thin, sweating white male in acute distress, unable to stand and complaining of pain in the left hip The outstanding physical finding was a large mass palpable deep in the left lower quadrant of the abdomen, arising from the pelvic brim and extending up to the left iliac

crest The mass was hard and non-tender, 10 cm in diameter, and seemed *attached to the bony pelvis The overlying skin was red and hot and contained* many dilated superficial venules A loud systolic bruit could be heard over the mass with the aid of a stethoscope At the site of the original biopsy scar, a doughy, orange-size, bluish mass could be seen

Laboratory examination revealed a moderate anemia, a white blood cell count of 7500 per cu mm with a differential that was unremarkable except for the presence of one plasma cell. There was 2 plus albuminuria but no Bence Jones proteinuria The erythrocyte sedimentation rate was 101 mm per hour The serum calcium was 13 3 mg. per cent; phosphorus 1.4 mg per cent; serum albumin 1 6 Gm per cent, and globulin 6.9 Gm per cent The electrophoretic analysis showed that 54 3 per cent of the total protein consisted of gamma globulin (table 8, case 8) Roentgen examination of the skeleton showed a large area of destruction in the left wing of the ilium (fig. 20), destruction of the bodies of D 4 and D 11, and multiple rarefactions in the ribs Sternal marrow yielded 28 per cent myeloma cells and aspiration of the mass in the *ilium yielded sheets of cells which were identical to those of the sternal marrow* and which were interpreted as myeloma cells

Within ten days of starting radiotherapy, marked diminution in pain and in the size of the mass occurred with loss of the systolic bruit The patient was ambulatory on discharge, but x-ray examination at that time showed no recalcification of the lesion in the pelvis

He was readmitted four months later because of the sudden development of weakness in both legs and inability to urinate. He had a paraplegia with a [illegible] tender mass

[illegible] otherapy

[illegible]

Postmortem examination revealed widespread multiple myeloma involving the bones (vertebrae, sternum, ribs, ilium, and femur), soft tissues, including the retroperitoneal, perirenal, and periadrenal tissues, the bladder wall, and lymph nodes (cervical, periaortic, and peripancreatic) Chronic right pyelonephritis with narrowing of the right ureter by tumor tissue was also present Considerable difficulty was encountered in differentiating the cell type found in the lymph nodes, which closely resembled reticulum cell sarcoma, from the invading myeloma cells of the tumor of the ilium In some areas, however, the iliac mass contained many cells similar to mature plasma cells (fig 4a)

A similar problem was encountered in the following case of multiple myeloma with generalized visceral infiltration, tumor nodules in the skin, jaundice, and purpura.

F. B, #562988, a 65 year old white female, complained of weakness for one [illegible] for six [illegible] ition [illegible] age [illegible] licus

and the spleen was huge, extending down to the iliac crest The skin was markedly icteric with many subcutaneous ecchymoses

The patient was severely anemic with 5 6 Gm per cent of hemoglobin and a red blood cell count of only 1 4 million per cu mm The white blood cell count



Fig 20 —Roentgenogram showing a huge myelomatous lesion of the wing of the ilium (Microscopic section of this tumor shown in figure 4*a*)

was 3450 per cu mm with 1 per cent myelocytes and 1 per cent plasma cells The platelet count was 8000 per cu mm The urine was positive for bile and there was a negative reaction for albumin and Bence Jones protein The serum albumin was 3 9 Gm per cent and the globulin 1 7 Gm per cent The alkaline phosphatase was 16 King-Armstrong units and the cephalin flocculation 4 plus

Bone x-rays demonstrated mottled areas of rarefaction in the skull and long bones Sternal marrow aspiration yielded characteristic myeloma cells

The patient remained in poor condition with profound anemia, leukopenia, and thrombocytopenia Ecchymoses and a large number of firm, subcutaneous, pea- to plum-size nodules were noted to appear on the arms, legs, and trunk. Two of the nodules, one from the thigh and the other from the trunk, were biopsied and reported to show reticulum cell sarcoma The patient died on the thirtieth hospital day

Postmortem examination showed multiple myeloma with generalized infiltration of the liver, spleen, and lymph nodes There was nodular infiltration of the diaphragm, *epicardium, lungs, liver, skeletal muscle, and subcutaneous* tissue The liver weighed 3300 Gm. and the spleen 1000 Gm. As in the previous case, the same difficulty arose in differentiating immature myeloma cell types seen in certain areas from what appeared to be reticulum cell sarcoma in other areas

The apparent similarity between multiple myeloma of this type and reticulum cell sarcoma has also impressed Bayrd.[18] He cites the case history of a 60 year old woman with osteolytic lesions, Bence Jones proteinuria, and hepatosplenomegaly who developed terminally a huge liver and flooding of the peripheral blood with many cells indistinguishable from reticulum cells. Impressed by the evident transition between reticulum cell, myeloma cell, and well differentiated plasma cell in this case, Bayrd could not escape the conclusion that the myeloma cell arose from the reticulum cell

Miscellaneous Signs and Symptoms

As mentioned above, low grade fever is not uncommon in multiple myeloma Thirty-nine per cent of the patients had temperature elevations from time to time rising to 101 F. rectally. An occasional patient developed febrile rises to as high as 102 or 103 F. for no known cause. With pneumonia, pulmonary infarctions, or incidental infections, still higher temperatures occurred, of course.

Abnormalities of the finger nails were occasionally noted. Two patients had definite clubbing of fingers and toes with broadening and floating of the nail-beds; three others had suggestive but not definite clubbing. One patient with severe hypochromic anemia and gastric achlorhydria had koilonychia. Another unexplained and not uncommon finding in patients with multiple myeloma was the disappearance of the lunulae from the base of the nails.

In long standing cases, signs of rheumatoid arthritis, even of osteoarthritis, may develop In many such cases the articular changes are due to deposition of amyloid within or about the synovial membrane of the joints.

5. ROENTGENOLOGIC CHANGES IN THE BONES

The classical x-ray finding in multiple myeloma consists of innumerable punched out areas of destruction involving many bones. These purely osteolytic areas are characteristically sharply demarcated and are most easily seen in the skull (fig 21). The roentgen picture of metastatic carcinoma, metastasizing thyroid adenoma (fig 22), and reticulum cell sarcoma (fig 23) may be identical Even the pseudocystic lesions of polyostotic fibrous dysplasia may cause differential diagnostic difficulties (fig 24) Thus, a sharply outlined, round or oval osteolytic lesion may or may not be a myeloma. In general, it can be stated that if the margin of the osteolytic lesion is fuzzy, the diagnosis of myeloma is unlikely It is indeed exceedingly rare to see any significant degree of osteoblastic reaction about the lesions The presence of such sclerotic bone change, unless merely due to condensation of surrounding bone, should cast doubt on the diagnosis of myeloma, or an associated lesion should be suspected The presence of periostitis is also very infrequent One patient (described on p 33) with a large destructive lesion of the vertebral column, which proved on biopsy to be a plasmocytoma, had, in addition, a lytic lesion in the ilium surrounded by a thin zone of sclerotic bone Biopsy of this lesion revealed, on section, not a myeloma, but an isolated lipoid granuloma (fig 25) Two patients had the unusual roentgenographic picture of Paget's disease and myeloma involving the same bone (fig 26) In one patient, the Paget lesion of the vertebral column had produced the picture of an ivory vertebra which stood out in marked contrast to the osteolytic lesions caused by myeloma Rare cases of myeloma with new bone formation occur [94,]

Diffuse demineralization of the skeleton is a common finding in myeloma The vertebral column, in particular, demonstrates this

(*Text continued on page 54*)

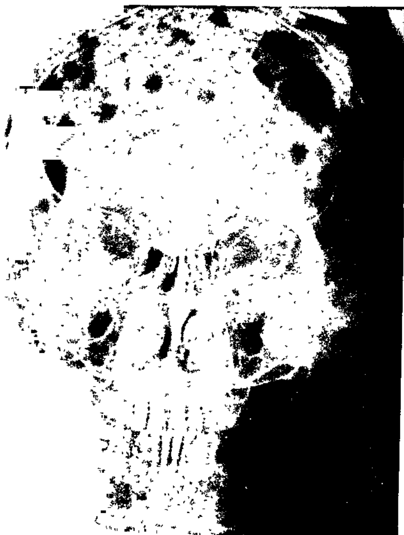


FIG 21 —Typical lytic lesions of multiple myeloma producing punched out destructive areas throughout the skull.

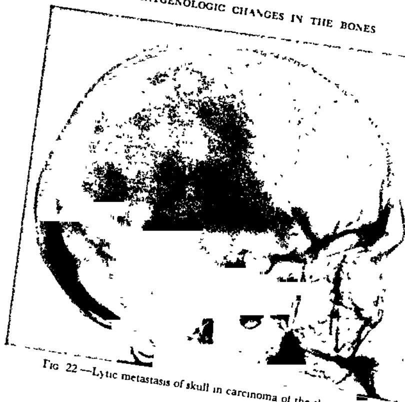


FIG 22.—Lytic metastasis of skull in carcinoma of the thyroid



FIG 23 —Punched out lesions of skull seen in reticulum cell sarcoma, simulating multiple myeloma



Fig 24 —Cystic lesion of calvarium in polyostic fibrous dysplasia



FIG. 23 —Punched out lesions of skull seen in reticulum cell sarcoma, simulating multiple myeloma

tumor of bone (fig. 29). It should be stressed that when a lesion resembling a giant cell tumor is found in a flat bone, where giant-cell tumors are unusual, myeloma or a lipoid granuloma should be suspected (fig. 25)

Geschickter and Copeland[66] found the lesions to be most commonly



Fig 26 —Simultaneous involvement of femora by multiple myeloma and Paget's disease

located in the spine, ribs, sternum, and clavicle, with the skull and the extremities near the pelvis or shoulder girdle forming a group that were involved about half as frequently The distribution of lesions in our series seemed to adhere to such a rule We have, in addition, noted involvement of the mandible in twelve cases The mandible is frequently involved, because it is a flat bone, which, even in adults, usually contains red marrow. On occasion we have seen lesions in almost every bone of the body including the small bones of the hands and the feet

Seven of the cases demonstrated no discrete lesion other than a

change and vertebral collapse (figs. 8, 9, 38) is extremely common. Many patients will present this finding in association with numerous areas of rarefaction, but it is surprising how frequently diffuse decalcification of the bones exists in the complete absence of any demonstrable focal lesions on the x-ray films.



FIG 25 —Rarefied area of ilium surrounded by rim of dense sclerosis in patient with proven myeloma of spine Biopsy of this lesion showed lipoid granuloma of bone

The destructive lesions (fig. 27) vary in size from 1 to 2 mm in diameter on up to extensive areas of bone dissolution the size of an orange or grapefruit (fig. 20). The smallest, when numerous, give the bones a sieve-like appearance which has been likened to a leopard skin or even to the interior of a bee hive (fig 28) The largest were seen to occur in the pelvis. Lesions are characteristically located in the medullary cavity of the bones and not infrequently erode through the cortex from within. Occasionally, large tumor deposits produce a soap bubble effect, sometimes simulating the appearance of giant cell



Fig 29 —Pathologic fracture through a "soap bubble" lesion produced by myeloma

diffuse, generalized demineralization, more marked in the spine, ribs, and pelvis Five of the patients, moreover, showed no demonstrable roentgen changes at all in the skeleton A series of such cases has been reported by Wallerstein.[204] An excellent paper by Heiser and Schwartzman,[78] in the radiologic literature, illustrates side-by-side the roentgen films and pathologic specimens of the various types of myelomatous bone lesions

FIG. 27.—Humerus riddled with destructive lesions of multiple myeloma.



FIG 28.—Healing fracture of femur with abundant callus formation Note the sieve-like appearance of the bone and the apparent myelomatous involvement of the callus itself.

precipitate will form between 44 and 50 C, and will later dissolve when heated above 95 C. If albumin is also present, it will be necessary to filter the boiling urine through a hot filter and then to note whether a precipitate forms as the urine cools It is interesting to read that in his original report on the properties of this substance, Bence Jones himself did not require it to precipitate at 40 to 60 C His description merely mentioned the precipitate caused by the addition of nitric acid to the urine, the disappearance of the precipitate on boiling, and its reappearance on cooling, a method which we would scarcely accept today as sufficient to demonstrate Bence Jones protein to the exclusion of proteoses and pseudo Bence Jones protein

Because it is often difficult to separate the albumin from the Bence Jones protein, a modification of this technic has been suggested by Jacobson and Wilner [83] Ten c c of fresh urine are adjusted to a pH of 5 5, heated to approximately 60 C., and held at this temperature for 10 minutes The urine is then centrifuged and decanted The precipitate, which contains the Bence Jones protein, is suspended and partly dissolved in 10 cc of normal urine Ten drops of concentrated nitric acid are added since Bence Jones protein only dissolves on boiling if the acidity is sufficiently high The suspension is then heated to boiling for ten minutes and filtered while hot When Bence Jones protein is present, all or nearly all the protein will dissolve during boiling and appear again on cooling

Bence Jones proteinuria is almost pathognomonic of multiple myeloma It has been reported in isolated instances of chronic lymphatic or myeloid leukemia, metastatic carcinoma of bone, sarcoma of bone, polycythemia vera, senile osteoporosis, and fibrocystic disease of bone Nearly all these cases are open to question since the abnormal urinary protein may actually have been pseudo Bence Jones which precipitates at 50 C but does not dissolve at 95 C or a proteose which does not precipitate below 60 C, but does dissolve at the boiling point In addition, it seems possible that some of the cases of "lymphatic leukemia" with Bence Jones proteinuria may actually have been cases of plasma cell leukemia It has already been brought out that it is sometimes difficult to differentiate myeloma cells in the peripheral blood from lymphocytes

In forty-eight of ninety-seven consecutive cases of this series, Bence Jones protein appeared sooner or later in the urine (49 per cent) Of these, four were negative at first, but became positive later in the

6. METABOLIC ABNORMALITIES IN MULTIPLE MYELOMA

Bence Jones Proteinuria

The excretion of Bence Jones protein in the urine is a unique characteristic of multiple myeloma. It may be excreted in huge quantities. Bence Jones,[21] in his original publication, reported an excretion of 60 Gm per day and Magnus-Levy[117,118] mentions that fourteen observations of a daily elimination of 30 to 77 Gm of Bence Jones protein can be found in the literature One patient of Dent and Rose[48,49] excreted about 36 Gm daily. The exact nature of Bence Jones protein has never been determined, and its relationship to the abnormal serum proteins and amyloid deposits is still a matter for conjecture. Bence Jones protein differs from other proteins in that it contains at best only traces of methionine and of hydroxy-proline

When the sulfosalicylic acid test is negative, no Bence Jones protein is present in the urine. The difficulties start, however, when proteinuria is found and the question arises as to whether part of the protein is Bence Jones protein A good method for screening cases for the presence or absence of Bence Jones proteinuria is to layer the urine over a few cc of concentrated hydrochloric acid. If no white ring forms at the interphase, Bence Jones protein cannot be present and more elaborate tests are unnecessary If a white ring does form, Bence Jones protein *may* be present, but since globulins, proteoses, and pseudo Bence Jones protein are also precipitated by this technic, further testing is then necessary. A 10 cc. sample of fresh urine is acidified with 2 per cent acetic acid until it reaches a pH of 5 5. Two cc. of saturated sodium chloride solution are added. The urine is then heated in a water bath, rather than over an open flame, since direct heating often alters the proteins. If Bence Jones protein is present, a

other words, the precipitation of the protein is incomplete at a concentration of 21 5 per cent sodium sulfate In such cases, the quantity of Bence Jones protein, which remains in solution during Howe fractionation, is erroneously calculated as albumin. In other instances, a slight precipitation occurs with a concentration of 17 4 per cent of sodium sulfate corresponding to pseudoglobulin II. However, a concentration of 13 per cent of sodium sulfate, which precipitates euglobulin, never causes any precipitation of Bence Jones protein. Thus, an increase of the euglobulin fraction of the serum determined by Howe fractionation can never be due to the presence of Bence Jones protein.

Comparable variations are encountered during the electrophoretic analysis of the Bence Jones protein. Rundles found that the electrophoretic mobility of the Bence Jones protein of his patients varied between 1 2 and 4 1 (p 74) Ten Thije[132a] noted electrophoretic mobilities between 0 8 and 3 8—that is, between the speed of alpha-2 globulin and that of the gamma fraction.

Bence Jones protein has allegedly been found in the blood,[53,85,131,171] in pericardial fluid,[12,171] in pleural fluid,[12,122] and even in spermatic fluid [7,21] Such findings, indicating the presence of measurable quantities of Bence Jones protein in body fluids other than urine, must be questioned, unless refined physicochemical methods have been used

For many years immunologic methods have been used in an effort to identify the abnormal proteins found in multiple myeloma. As early as 1911, Massini[125] devised serologic technics to distinguish Bence Jones protein from the normal serum protein These findings were first confirmed and further developed by Bayne-Jones and Wilson,[17] and later by Hektoen and Welker [76] The antigenic properties of Bence Jones protein may be studied rather easily since this protein can often be crystallized in antigenically pure form In order to obtain an antiserum, rabbits must be injected with large quantities of Bence Jones protein, because the latter is only weakly antigenic In this way it has been possible to demonstrate that there are at least two serologically different Bence Jones proteins In 1943, Moore, Kabat, and Gutman[131] were able to demonstrate the protein in the sera of patients by using antisera, prepared against the Bence Jones protein of these patients It should be emphasized that it has never been possible by immunochemical methods to find more than 0 2 Gm. of Bence Jones protein per 100 cc. serum Nevertheless, in an occasional case, the protein has been demonstrated by either electrophoresis or ultra-

disease In one instructive case a patient maintained normal renal function for a long period of time until Bence Jones protein appeared in his urine, at which time progressive renal insufficiency ensued When all the cases in this series have been followed to their terminal outcome, a higher percentage of positive reactions will undoubtedly be found.

Bence Jones protein is a substance of relatively low molecular weight, which, when measured by ultracentrifugation, usually ranges from 35,000 to 40,000 with extremes of 24,000 to 90,000 [154,196] Since Bence Jones protein has such a low molecular weight, it is easily filtered through the normal glomerulus Magnus-Levy believes that Bence Jones protein, like the abnormal myeloma globulins, is formed by the myeloma cells in the bone marrow. Meyler,[128] on the other hand, contends that this protein is formed in the normal bone marrow in minute quantities, so small as not to be detected in normal sera or urine. In myeloma, the production of Bence Jones protein would then become so great as to be excreted in recognizable amounts in the urine. Apitz[8] concluded that the myeloma cells produce a whole range of abnormal proteins, all of which are "blood foreign" leading to "paraproteinemia " Because of this quality they are excreted by the *kidneys ("paraproteinuria"), partly as Bence Jones protein, partly* as proteins of higher molecular weight. In other cases this abnormal protein is deposited in the tumor tissue and in various organs and tissues in the form of paramyloid ("paraproteinosis").

The relation between Bence Jones protein as it is excreted in the urine and the abnormal serum proteins of multiple myeloma has been the subject of much thought and investigation Combined electrophoretic, ultracentrifugal, and immunochemical technics have added much information, but the final answer is still not at hand. The study of purified Bence Jones protein isolated from the urine of patients with multiple myeloma indicates that concentrations of magnesium and sodium sulfate, at which Bence Jones protein precipitates, may vary considerably from case to case. Ten Thije,[192a] using the method of Derrier, found that four of five true Bence Jones proteins were precipitated by phosphate concentrations between 49 and 59 per cent. Precipitation of Bence Jones protein in the urine with ammonium sulfate usually starts at a concentration of 40 $\pm$ 2 per cent and is complete at 50 $\pm$ 5 per cent. On Howe fractionation Bence Jones protein, in some instances, behaves like albumin; in

when Bence Jones protein was present in the urine. However, when there was no Bence Jones protein in the urine, the average serum globulin was considerably higher—4 6 Gm per cent.

Analyzing forty-four of our cases in whom electrophoretic separation of the different globulin fractions was performed, the following data were obtained Bence Jones proteinuria was found in one of four cases with alpha globulinemia, in two of six cases with beta globulinemia, and in four of twenty-one cases with gamma globulinemia In contrast, ten of thirteen cases in whom the electrophoretic pattern showed only minor anomalies had Bence Jones proteinuria

The explanation for this inverse relationship between Bence Jones proteinuria and hyperglobulinemia is not clear. It may be due to the fact that when a high serum globulin level exists, the small Bence Jones molecule becomes involved in a complex formation with the high molecular weight serum globulins After combining with these large molecules, Bence Jones protein cannot be filtered through the glomerulus [131] On the other hand, the loss of large quantities of Bence Jones protein in the urine may serve to reduce the serum protein in much the same way that heavy albuminuria serves to reduce the serum albumin in the nephrotic syndrome

Abnormalities of Serum Protein

One of the most intriguing phenomena of multiple myeloma is the elaboration of abnormal serum proteins The opinion of Magnus-Levy[117,118] that these abnormal proteins are the product of the myeloma cells in the bone marrow has already been mentioned Numerous observations have confirmed his impression that a relation between plasma cells and serum globulins exists Bing and Plum[30] have pointed out that an increase of plasma cells and reticulum cells is a feature common to various diseases with hyperglobulinemia Bjorneboe and Gormsen[31] produced tissue infiltration with plasma cells by repeated immunization of rabbits with killed pneumococci and noted a definite elevation of the serum globulin proportional to the degree of plasma cell infiltration Fagreaus[60] demonstrated in rabbits, which were sensitized to horse serum, that hyperglobulinemia developed concomitantly with a proliferation and maturation of plasma cells from the reticulum cells of the bone marrow. Pariser and his associates,[138] extending these studies to human subjects, immunized twelve Schick negative adult males with diphtheria toxin Most of these subjects

centrifugation Collier et al [39] have also prepared Bence Jones antiserum by repeatedly injecting protein into rabbits. This rabbit serum, containing the Bence Jones antibodies, is said to be capable of demonstrating minute quantities of Bence Jones protein in both urine and blood In fact, these workers discovered the presence of Bence Jones protein in the urine of ten patients with myeloma, who had negative

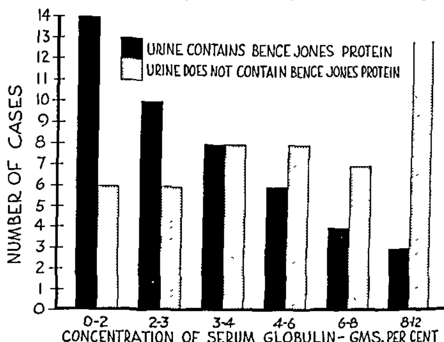


FIG 30—Inverse relationship between Bence Jones proteinuria and hyperglobulinemia

chemical tests for Bence Jones proteinuria. Several "solitary plasmacytomas" were found to have positive tests by this method. These results have yet to be confirmed.

It has been pointed out by others,[1,117,211] that Bence Jones proteinuria occurs more commonly in the absence of hyperglobulinemia than in its presence. Our experience confirms this point of view, although exceptions exist (table 9). An analysis of the relationship of the serum globulin level to the presence or absence of Bence Jones proteinuria showed a definite tendency for the serum globulin to be lower when Bence Jones protein was being actively excreted in the urine (fig. 30) The average serum globulin, determined with the Majoor modification[120] of the Howe method was 3 0 Gm. per cent

when Bence Jones protein was present in the urine. However, when there was no Bence Jones protein in the urine, the average serum globulin was considerably higher—4.6 Gm per cent.

Analyzing forty-four of our cases in whom electrophoretic separation of the different globulin fractions was performed, the following data were obtained Bence Jones proteinuria was found in one of four cases with alpha globulinemia, in two of six cases with beta globulinemia, and in four of twenty-one cases with gamma globulinemia In contrast, ten of thirteen cases in whom the electrophoretic pattern showed only minor anomalies had Bence Jones proteinuria

The explanation for this inverse relationship between Bence Jones proteinuria and hyperglobulinemia is not clear. It may be due to the fact that when a high serum globulin level exists, the small Bence Jones molecule becomes involved in a complex formation with the high molecular weight serum globulins After combining with these large molecules, Bence Jones protein cannot be filtered through the glomerulus [151] On the other hand, the loss of large quantities of Bence Jones protein in the urine may serve to reduce the serum protein in much the same way that heavy albuminuria serves to reduce the serum albumin in the nephrotic syndrome

Abnormalities of Serum Protein

One of the most intriguing phenomena of multiple myeloma is the elaboration of abnormal serum proteins The opinion of Magnus-Levy[117,118] that these abnormal proteins are the product of the myeloma cells in the bone marrow has already been mentioned Numerous observations have confirmed his impression that a relation between plasma cells and serum globulins exists Bing and Plum[30] have pointed out that an increase of plasma cells and reticulum cells is a feature common to various diseases with hyperglobulinemia Bjorneboe and Gormsen[31] produced tissue infiltration with plasma cells by repeated immunization of rabbits with killed pneumococci and noted a definite elevation of the serum globulin proportional to the degree of plasma cell infiltration Fagreaus[60] demonstrated in rabbits, which were sensitized to horse serum, that hyperglobulinemia developed concomitantly with a proliferation and maturation of plasma cells from the reticulum cells of the bone marrow. Pariser and his associates,[138] extending these studies to human subjects, immunized twelve Schick negative adult males with diphtheria toxin Most of these subjects

showed typical and atypical plasma cells in the peripheral blood on or about the seventh day following immunization. At the same time four of the twelve showed an increase in the plasma cell content of the sternal bone marrow. The individuals whose antitoxin response was most marked were the ones who reacted with a significant proliferation of plasma cells in the bone marrow. The greater part of these cells were typical plasma cells of the Marschalko type, with cartwheel arrangement of the nuclear chromatin, but immature cells were also found.

Rundles' observations on urethane treated myeloma patients[155] seem to confirm Magnus-Levy's conclusion that the abnormal proteins found in multiple myeloma are the product of the abnormal plasma cell proliferation in the marrow. He noted that when, under influence of urethane, a reduction in the number of myeloma cells occurred within the marrow, a decrease in abnormal serum globulins and Bence Jones proteinuria followed shortly thereafter. When urethane produced no effect on the marrow, no decrease of the abnormal proteins could be detected.

After extraction of myeloma tissue with saline, Martin[124] obtained a protein, the electrophoretic and ultracentrifugal patterns of which corresponded to those of the abnormal globulins present in the serum.

Lane[101] has made an interesting observation which, if confirmed, may well be crucial in determining whether the abnormal proteins are produced by myeloma tissue. He reported the return of the serum globulin to normal after the resection of an isolated plasmocytoma of the mandible (p 100).

Fractionation of the sera of myeloma patients by salting out with ammonium sulfate indicates that the abnormal proteins found in such sera belong to the globulin fraction. Howe, using the sodium sulfate fractionation, designated the fractions as follows:[81] 13.5 per cent sodium sulfate precipitates euglobulin (0.1 to 0 4 Gm. per cent); 17 4 per cent sodium sulfate precipitates pseudoglobulin I (0.8 to 1.9 Gm. per cent); 21.5 per cent sodium sulfate precipitates pseudoglobulin II (0 2 to 0.8 Gm. per cent)

The albumin fraction (4.7 to 5 2 Gm per cent) remains in the filtrate following the 21.5 per cent sodium sulfate precipitation. There is little doubt that this Howe fractionation is a crude method. It yields results which are too high for the albumin content of the serum, because this method of fractionation leaves in solution, not only albumin, but also alpha globulin.

Levin et al.[103] have reviewed the various modifications of the salting out methods which produce more homogeneous fractions and correlate more closely with electrophoresis. Several recent modifications by Majoor[120] and Milne[130] have increased the value of the Howe procedure by improving its correlation with electrophoresis Majoor precipitates the euglobulin fraction with 18.5 per cent sodium sulfate and the pseudoglobulin fraction with 26 8 per cent sodium sulfate The filtrate remaining after the last precipitation contains the albumin fraction.

In the quantitative determination of the total protein content of the serum and the albumin-globulin ratio, the most accurate results can be obtained by use of the Kjeldahl or micro Kjeldahl technics The biuret method is also quite good, but because of the nature of the abnormal proteins in myeloma sera, the tyrosine method gives very poor results. Using the Majoor modification of the original Howe method, we found that in ninety-seven consecutive cases of multiple myeloma the total protein of the serum was elevated above 8 Gm per cent in 72 per cent of the cases. This is slightly higher than the figures usually recorded in the literature. In 45 per cent of these cases the serum globulin exceeded 7 Gm per cent. In three patients the serum globulin ran as high as 11 3, 11.1, and 10.1 Gm. per cent respectively In several cases the albumin-globulin ratio was actually reduced to less than 1:10

The hyperglobulinemia of myeloma patients differs from the hyperglobulinemia found in many other diseases, such as acute lupus erythematosus, subacute bacterial endocarditis, Boeck's sarcoidosis, liver cirrhosis, schistosomiasis, leprosy, kala-azar, etc In the latter group of diseases, the hyperglobulinemia is almost always due to an increase of the euglobulin plus the pseudoglobulin I fractions in a fairly uniform proportion. This happens only occasionally in multiple myeloma,[71] where usually either the euglobulin fraction alone or one of the pseudoglobulin fractions is increased Occasionally, the euglobulin and the pseudoglobulin II fractions are both elevated or pseudoglobulin I and II are increased together. Thus, fractionation of the serum proteins by one of the modern modifications of the Howe method often reveals a pattern of the serum globulin fractions which differentiates myeloma from those other diseases in which increased serum globulin is found

Table 4 demonstrates the partition of pseudoglobulin and euglobu-

lin by the original Howe method, in seven consecutive cases of multiple myeloma with hyperglobulinemia These cases were observed by one of us elsewhere [177]

TABLE 4 —*Results of Howe Fractionation of the Serum in Seven Cases of Multiple Myeloma*

	Total Protein (in Gm %)	Albumin (in Gm %)	Pseudoglobulin (in Gm %)	Euglobulin (in Gm %)	Bence Jones Protein in Urine
Normal	6 5–7 9	4 7–5 7	1 2–2 1	0 2–0 4	
Case 1	13 6	1 9	1 6	9 7	++
Case 2	8 8	2 7	0 9	5 6	– –
Case 3	10 7	3 6	0 9	4 9	– –
Case 4	9 1	3 5	2 6	2 6	– –
Case 5	10 3	3 9	5 3	0 4	– –
Case 6	9 9	3 4	5 7	0 3	++++
Case 7	10 3	2 6	7 5	0 2	+

All these cases had hypoalbuminemia Three of these cases reveal a considerable increase of the euglobulin fraction with normal pseudoglobulin figures Three other cases show exactly the opposite, that is, an increase of the pseudoglobulin with a normal euglobulin fraction The results of the Howe determination in these six cases, therefore, indicate that the hyperglobulinemia is probably due to myeloma Only in case 4 is the result doubtful, because here, though the euglobulin content is very much increased (2 6 Gm per cent), the pseudoglobulin content is also moderately increased (2 6 Gm per cent). Unfortunately, at the time these seven patients were studied, electrophoresis was not yet available

The cephalin flocculation and thymol turbidity tests are not necessarily positive in myeloma as they are in most other conditions associated with hyperglobulinemia This has also been noted by Kunkel and Hoagland [97] The Takata Ara reaction is usually positive when the increase is due to euglobulin, but not when due to pseudoglobulin I. The formol gel test is positive when the serum globulin rises above 3 6 Gm per cent, irrespective of the globulin fractions involved. This test is performed by adding two large drops of 40 per cent formalin to 1 cc of serum, and it is positive if the serum gels within a period of twenty-four hours. In many instances of marked hyperglobulinemia the gel forms so quickly and is so viscid, that the test tube can be

inverted immediately after the formalin is added without spilling its contents. In our experience it is a simply performed and an unusually reliable test for hyperglobulinemia; it was positive in fifty-four of the eighty-five cases in which it was carried out (63 per cent). In our series there was only one false negative formol gel test in a patient with a globulin of 3.9 Gm per cent There was also one false positive reaction in a patient with a serum globulin of only 2 5 Gm. per cent.

Sia's dilution test is another simple procedure which can detect an elevation of the euglobulin content of the serum This test is carried out by drawing up 20 cu mm of blood in a hemoglobin pipet, emptying it immediately into 0 6 cc of distilled water in a small test tube and mixing briefly The tube is allowed to stand vertically and the test is positive if turbidity appears within 5 minutes The test can be graded 1 to 4 plus on the basis of the amount and rapidity of settling of the sediment in the course of an hour. In the forty cases in which the test was carried out the reaction was positive in 32 per cent Regardless of which method is used to determine the globulins, marked differences can be noted between the globulins of myeloma sera and those of the sera of normal persons or of nonmyelomatous patients with hyperglobulinemia

Cryoglobulinemia

Much attention has recently been given to the study of cryoglobulins, that is, globulins which precipitate at a low temperature. Although a few cases have been observed in other conditions such as chronic arthritis, periarteritis nodosa, and subacute bacterial endocarditis, the majority of cases of cryoglobulinemia reported in the literature[15,134,150] have occurred in patients with multiple myeloma. Despite this fact, cryoglobulinemia is so rare that it is even unusual in myeloma [15] It was sought for in seventeen cases in this series, but it could be found in only one Most cases of myeloma with cryoglobulinemia show a hemorrhagic tendency and purpuric skin lesions The latter are mainly localized in the parts of the body which are exposed to cold Microscopically, a precipitation of protein is found in the blood vessels of the skin Rorvik[150] described a most unusual case of cryoglobulinemia in a 56 year old farmer with purpura and marked sensitivity to cold, whose blood actually congealed in the needle as it was drawn from the vein and whose serum stiffened into a viscid grey-white substance at room temperature At autopsy there was diffuse myelomatosis. Hill et al [80] described the presence in a proven

case of myeloma of a lipoprotein, which they called a "cryoprotein" This substance solidified on cooling, gave the characteristic reactions of protein, and, when purified by repeated reprecipitation, separated out as needle-like crystals of a cholesterol ester.

Electrophoresis

Electrophoresis has been of the greatest help in clarifying several problems in this field. It is possible to determine the speed with which electrically charged particles in general and protein particles in particular migrate in a buffer solution under the influence of an electric current. Proteins always travel in the direction of the cathode, but the speed of this so-called electrophoretic migration is different for different protein fractions.

In order to calculate the speed with which a protein fraction moves, the distance from the starting point of migration to the maximum ordinate of the respective peak is carefully measured in centimeters The mobility of each fraction is then expressed in terms of $10^{-5} \times cm.^2 \times seconds^{-1} \times volt^{-1}$.

The albumin fraction has the greatest velocity From their successively slower speed of migration one can differentiate between alpha-1 globulin (rich in glycoproteins and lipoproteins), alpha-2 globulin (rich in glycoproteins and mucoproteins), beta globulin (rich in lipids and lipoproteins) and gamma globulin (which, at least in normal serum, contains the bulk of the antibodies)

The designations of the various protein fractions, calculated according to the speed of migration during electrophoretic fractionation, are defined differently by different authors. Rundles and his associates define protein fractions moving with a velocity of 0 3 to 1 7 as gamma globulin, whereas their beta globulins have a velocity of more than 2 6. Stern and Reiner,[187] using a more liberal definition of the different fractions, designate any fraction migrating with a mobility of 0.0 to 2 5 $\times 10^{-5}$ as a gamma globulin type; 2.5 to 3 6 $\times 10^{-5}$ as a beta globulin type, 3.6 to 4.5 $\times 10^{-5}$ as an alpha globulin type. Therefore, a fraction which is defined in Stern and Reiner's system as a gamma type may have a mobility which deviates from gamma globulin as defined, for instance, by Rundles. The same holds true for the alpha and beta globulins.

Using their nomenclature, Stern and Reiner[146, 187] found, in normal and healthy persons, that about 60 per cent of the total serum proteins

belong to the albumin fraction, 7 per cent belong to the alpha-1 globulin, 9 per cent to the alpha-2 globulin, 13 per cent to the beta globulin, and 14 per cent to the gamma globulin fraction. Under this simplified nomenclature, Reiner and Stern[146] found, among ninety-one myeloma patients, that 6.6 per cent were of the alpha type, 15.4 per cent were of the beta type, 55 per cent were of the gamma type, and 22 per cent had minor anomalies. It should be noted that under their system patients with the so-called M fraction are included in either the beta or gamma types of patterns. These investigators have set these arbitrary limits in order to emphasize that although a fraction of myeloma serum migrates with the same mobility as normal alpha, beta, or gamma globulin, it may have entirely different physicochemical characteristics.

The great value and accuracy of electrophoresis in the study of myeloma sera has been reported by Gutman et al.,[70,131] Adams, Alling, and Lawrence,[1] Lewis, Bortz, and Battle,[104] Stern and Reiner,[146,167] Rundles, Cooper, and Willett,[154] Waldenström,[201] Janssen,[85] and others[132,134,135] In contrast to other diseases associated with hyperglobulinemia, the abnormal globulin in myeloma appears as a high, sharp spike on the electrophoretic pattern (fig. 31). In nearly all cases where hyperglobulinemia was found, a decrease of the albumin fraction was also observed. Gutman and his associates reported that there are four major electrophoretic patterns which characterize myeloma sera:

1. A large serum component with the mobility of normal gamma globulin which usually, but not always, corresponds, on Howe fractionation, to a high euglobulin precipitation

2. A definite increase in the fraction which moves with the speed of normal beta globulin and which, on Howe fractionation, often corresponds to pseudoglobulin I.

3. A component with a mobility comparable to that of fibrinogen, that is, slower than normal beta globulin, but faster than gamma globulin. This fraction has been designated by Gutman and his associates[131] as the M component.

4 A pattern with no characteristic change from the normal.

Whereas Rundles and his associates also recognize the M component of Gutman as a separate fraction, in Stern and Reiner's nomenclature the M component is designated as either beta or gamma globulin Wuhrmann et al.[217] distinguish between a beta-1 and a beta-2

case of myeloma of a lipoprotein, which they called a "cryoprotein". This substance solidified on cooling, gave the characteristic reactions of protein, and, when purified by repeated reprecipitation, separated out as needle-like crystals of a cholesterol ester.

Electrophoresis

Electrophoresis has been of the greatest help in clarifying several problems in this field. It is possible to determine the speed with which electrically charged particles in general and protein particles in particular migrate in a buffer solution under the influence of an electric current. Proteins always travel in the direction of the cathode, but the speed of this so-called electrophoretic migration is different for different protein fractions.

In order to calculate the speed with which a protein fraction moves, the distance from the starting point of migration to the maximum ordinate of the respective peak is carefully measured in centimeters. The mobility of each fraction is then expressed in terms of $10^{-5} \times cm^2 \times seconds^{-1} \times volt^{-1}$.

The albumin fraction has the greatest velocity. From their successively slower speed of migration one can differentiate between alpha-1 globulin (rich in glycoproteins and lipoproteins), alpha-2 globulin (rich in glycoproteins and mucoproteins), beta globulin (rich in lipids and lipoproteins) and gamma globulin (which, at least in normal serum, contains the bulk of the antibodies).

The designations of the various protein fractions, calculated according to the speed of migration during electrophoretic fractionation, are defined differently by different authors. Rundles and his associates define protein fractions moving with a velocity of 0.3 to 1.7 *as gamma globulin, whereas their beta globulins* have a velocity of more than 2.6. Stern and Reiner,[187] using a more liberal definition of the different fractions, designate any fraction migrating with a mobility of 0.0 to 2.5 $\times 10^{-5}$ as a gamma globulin type; 2.5 to 3.6 $\times 10^{-5}$ as a beta globulin type; 3.6 to 4.5 $\times 10^{-5}$ as an alpha globulin type. Therefore, a fraction which is defined in Stern and Reiner's system as a gamma type may have a mobility which deviates from gamma globulin as defined, for instance, by Rundles. The same holds true for the alpha and beta globulins.

Using their nomenclature, Stern and Reiner[146,187] found, in normal and healthy persons, that about 60 per cent of the total serum proteins

fraction Their beta-1 fraction corresponds to the cases which other workers designate simply as beta fraction Their beta-2 fraction moves only slightly more speedily than the gamma fraction and most investigators include this beta-2 fraction with the gamma fraction. They found, among sixty myeloma patients, the following distribution: 10 alpha patterns, 10 beta-1 patterns, 15 beta-2 patterns, 23 gamma patterns, and 2 minor anomalies

The unusual observation of such a high percentage of sera with alpha patterns, which are encountered in this series, requires special discussion (p. 75). When the beta-2 patterns are counted as gamma patterns, then in this series, too, more than half of the myelomas show a marked increase of the gamma globulin fraction Janssen[88] found among thirty-seven myeloma patients, 5 beta patterns, 23 gamma patterns, and 9 minor anomalies

Rundles and his associates found abnormal serum proteins in twenty-five of their thirty myeloma patients They, like Waldenstrom, Olhagen, Janssen and many other workers, did not find any alpha globulin patterns Seventeen of Rundles' patients had abnormal protein fractions moving with the velocity of gamma globulin In eight cases the abnormal fraction had a mobility of 1 9 to 2 6, that is, an electrophoretic mobility between gamma and beta globulin comparable to the M fraction of Gutman and his associates. Many sera showed minor abnormalities such as a moderate increase in alpha globulins or irregular variations in beta lipoproteins.

Stern and Reiner found, among ninety-one myeloma patients,

---

cent) (table 12, #4)

umin

mmma

(*h*) Periarteritis nodosa Increase of gamma globulin (36 6 per cent) Albumin 2 7 Gm per cent, globulin 4 7 Gm per cent

(*i*) Multiple myeloma Low albumin Sharp peak of anomalous globulin (72 4 per cent) migrating at a speed between beta and gamma globulin (table 11, #4)

(*j*) Boeck's sarcoid Increased gamma globulin (30 1 per cent) Albumin 3 0 Gm

Gm per cent, globulin 5 7 Gm per cent

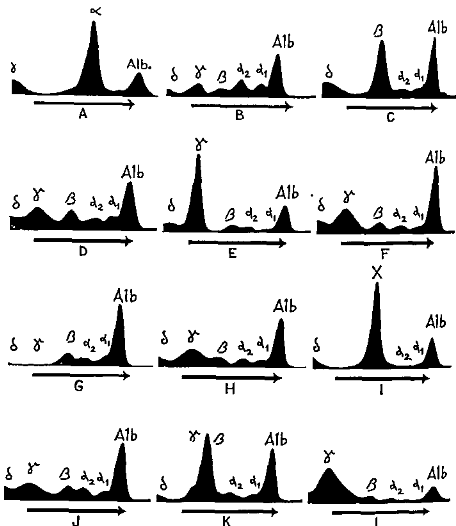


Fig 31 —Comparison of the electrophoretic patterns found in multiple myeloma and in other diseases with hyperglobulinemia

(*a*) Multiple myeloma Very large peak (74.8 per cent) migrating with the speed of alpha globulin Patient died with plasma cell leukemia.

(*b*) Nonsuppurative panniculitis Moderate increase in alpha-1 globulin (12 5 [illegible]

per cent)
) Gm per
cent)

(*e*) Multiple myeloma Low albumin Sharp peak of gamma globulin (62 1 per

clear—an indication that the beta globulinemia found in biliary cirrhosis and in myeloma are not identical. Only one instance of myeloma with beta globulinemia and lipemic serum has been mentioned in the literature.[201] The gamma peak found in most conditions with hyperglobulinemia is broad and low in contrast to the high sharp spike, which is commonly seen in multiple myeloma (fig. 31). Recently, however, we have seen an electrophoretic pattern with a high and sharp gamma globulin peak in a very sick child, suffering from disseminated histoplasmosis.

Several other findings may be cited as indicating clear-cut physicochemical differences between the abnormal globulins found in multiple myeloma and the increased serum globulins found in many other diseases The amino acid content of the gamma globulin of the myeloma patient differs from that of normal gamma globulins It is also significant that in myeloma sera, despite a high euglobulin or gamma globulin content, the bacterial antibody level may be decreased to a significant degree. In the opinion of Rohr[149] the replacement of a large part of the antibody producing reticuloendothelium of the bone marrow by myeloma tissue may be responsible for the decreased resistance of these patients to intercurrent infections, especially pneumonia

Wuhrmann and his associates[214] have observed that the greater the mobility of the myeloma protein during the electrophoresis, the further removed it is antigenically from normal gamma globulin Kunkel and his associates[93] demonstrated that antisera prepared from normal gamma globulin reacted with the special myeloma globulin found in the serum of four myeloma patients Nevertheless, myeloma gamma globulin should not be identified with normal gamma globulin, because the myeloma gamma globulin lacks some part of the antigenic properties of the normal gamma globulin As a result, it is difficult to prepare antisera against myeloma gamma globulin

This was further emphasized by Wuhrmann, Wunderly, and Hassig,[215] who recently prepared antisera against the concentrated globulins isolated from the sera of myeloma patients These authors were unable to prepare an antiserum when a myeloma serum with an increased gamma globulin fraction was used as an antigen They were more successful in four cases in which the beta globulin fraction of the serum was very much increased From these beta globulin sera, separate antisera were obtained, they precipitated, however, only the beta globulin of the myeloma serum from which the specific antiserum

6.6 per cent alpha patterns, 15.4 per cent beta patterns, 56 per cent gamma patterns, and 22 per cent minor anomalies.

Adams, Alling, and Lawrence[1] describe a pattern with a tall peak migrating even more slowly than gamma globulin, and they state that in their series, none of the myeloma sera had an electrophoretic pattern which they considered to be entirely normal. Rarely does a myeloma serum contain considerable amounts of two different abnormal fractions at the same time. Although the electropheretic gamma globulin fraction often corresponds to the Howe euglobulin fraction and the beta fraction to the Howe pseudoglobulin I, exceptions occur rather frequently One instance has been reported of a serum which appeared to contain a large pseudoglobulin I fraction on Howe fractionation, but which on electrophoresis, showed a large gamma peak In another case a large euglobulin fraction appeared during electrophoresis in the form of an M component. One case of multiple myeloma has been reported where 74 per cent of the total serum protein was present in the Howe albumin fraction, whereas 54 per cent was found in the albumin fraction on electrophoresis In another case the serum albumin value was calculated with the Howe method as 5 8 per cent; electrophoretically, a figure of 4.0 Gm per cent was obtained

Frequently Howe fractionation of a myeloma serum reveals a nearly normal protein spectrum, while electrophoretic analysis of the same serum reveals a distinctly abnormal pattern. Therefore, in doubtful cases electrophoresis as well as ultracentrifugation will have to be added to the Howe fractionation method in order to differentiate myeloma from other conditions with elevated serum globulin levels. In approximately half of the cases of multiple myeloma with hyperglobulinemia, electrophoresis reveals that the elevation of the serum protein is due to a fraction other than gamma globulin In contrast to this, the hyperglobulinemia of most nonmyelomatous conditions is only rarely due to a fraction other than gamma globulin. Only when there is an abnormality of lipoproteins, in biliary cirrhosis, nephrosis, and in some cases of leukemia, for example, may there be an elevation of the beta globulin

In biliary cirrhosis with beta globulinemia the serum is usually milky in appearance. This is understandable, since the beta fraction contains most of the lipoproteins. On the other hand, in cases of multiple myeloma with beta globulinemia, the serum is nearly always

One or more electrophoretic analyses of the serum were made in forty-four of the multiple myeloma patients in this series by Dr. *Miriam Reiner.* Alpha patterns were found in four patients, beta patterns in six patients, and gamma patterns in 21 patients In thirteen patients only minor abnormalities could be elicited It should be added that one of the four patients with alpha patterns showed an abnormal curve with an elevation of both alpha-1 and alpha-2 fractions. In this patient the diagnosis of multiple myeloma was probable, but not completely certain. The other three cases showed an increase of the alpha-2 peak alone

Alpha patterns. As mentioned above, Wuhrmann and his associates[217] found ten instances of alpha globulin patterns among sixty patients with multiple myeloma Study of their electrophoretic curves, however, seems to indicate that only three of these ten cases showed sharp alpha globulin peaks The electrophoretic curves of the other seven cases would perhaps better be designated as patterns with minor anomalies—with a slight to moderate increase of the alpha-1 and alpha-2 fractions (more than 11.4 per cent and 12 5 per cent re-

TABLE 5 —*Findings in Three Patients with Alpha Patterns on Electrophoresis of Serum*

	Date	Case	Albumin	Alpha-1	Alpha-2	Beta	Gamma	Urine Bence Jones	Total protein or Alb /glob (Gm per cent)
			(Per cent of total serum protein)						
1	10/14/48	Al	26 6	5 4	68 2	0	0	++	3 2/5 0
2a	9/1/49	Gu	20 6	2 8	74 8	0	1 8	Neg	2 8/7 5
2b	12/21/49	Gu	23 78	3 3	72 9	0	0	Neg	T P 10 3
3a	7/11/47	Li	45 5	6 8	28 9	11 2	8 1	Neg	5 4/3 1
3b	6/16/48	La	52 0	5 4	13 6	19 2	9 4	Neg	4 4/2 0

spectively) Lüdin's cases[114] of alpha globulinemia in myeloma should also be designed as examples of a minor anomaly. Sandkuhler[182] observed a myeloma patient in whom 53 per cent of the total protein moved, during electrophoresis, with the speed of alpha-2 globulin As mentioned above (p 71) other investigators have never found a case of multiple myeloma with a high alpha globulin content of the serum

In view of the rarity of alpha globulinemia in multiple myeloma,

had been prepared and not the beta globulins of other myeloma sera. Since such antisera are strictly individually specific, they cannot be used as a diagnostic test for multiple myeloma. Furthermore, the antisera prepared from the beta globulins of myeloma patients do not react with Bence Jones protein, either of the same patients or of other patients

Since the quantities of Bence Jones protein present in the serum never exceed 0.2 Gm. per cent (p 61), this abnormal protein could hardly account for the differences in the results obtained by Howe fractionation and electrophoresis. Moore and his coworkers[131] reported that by adding purified Bence Jones protein from the urine of a myeloma patient to the serum of a normal person, a myelomatous pattern could be produced in the normal serum with peaks corresponding in position to those in the serum of the myeloma patient from whom Bence Jones protein was obtained. They also demonstrated an electrophoretic correspondence between the Bence Jones protein excreted in the urine and the abnormal serum proteins, irrespective of whether the serum contained an excess of beta or gamma globulins

Such correspondence between the electrophoretic patterns of serum and urinary proteins is, however, no regular finding. Ten Thije[192a] found this only rarely among his patients with marked Bence Jones proteinuria Rundles, Cooper, and Willett[154] demonstrated that in only nine of seventeen cases with Bence Jones proteinuria did the urinary protein show the same electrophoretic mobility as the abnormal serum increment A somewhat greater mobility of the urinary protein was found in five patients, and in three other patients its mobility was much greater than that of the abnormal serum fraction They evidently did not find Bence Jones protein which migrated more slowly than the abnormal globulin in the serum of the patient. Other authors, however, have reported that a patient with beta globulinemia may excrete a Bence Jones protein which behaves electrophoretically as a gamma globulin and vice versa Rundles feels that the small sized Bence Jones urinary protein is derived from serum globulin increments of high molecular weight by a process of fragmentation of the larger molecule. Changes in surface charge coming about during the process of fragmentation may account for the faster electrophoretic mobility of some of their Bence Jones proteins.

curred At this time the serum albumin was found to be 2.8 Gm per cent, the globulin 7.5 Gm per cent and, on electrophoresis, 73 to 75 per cent of the total protein of the serum consisted of alpha-2 globulins The patient died in another hospital with the picture of plasma cell leukemia There was massive infiltration by myeloma cells of the visceral organs

In this connection it is interesting that Wuhrmann and his associates[217] have observed that the serum of patients with plasma cell leukemia usually shows either minor anomalies of the electrophoretic pattern or an alpha pattern. They state that plasma cell leukemia with a beta or gamma pattern is extremely rare Bichel and his colleagues[27] found only minor anomalies of the globulin pattern in their case with plasma cell leukemia Our patient with a marked alpha-2 globulinemia lends weight to these observations.

Four other cases with plasma cell leukemia were seen, but only one of these was studied electrophoretically The pattern of this patient showed only a very minor anomaly consisting of a slight increase of the alpha-2 globulin content to 9 2 per cent, which barely exceeds the upper limit of normal The electrophoretic patterns of our three other cases with plasma cell leukemia are not known Since two of these patients had normal serum albumin and globulin figures (3 6/1 3 and 4 4/2 2 respectively) it seems probable in the light of our experience, that their electrophoretic patterns must also have exhibited only minor anomalies Thus, of the five patients with plasma cell leukemia, one patient had minor anomalies of the electrophoretic pattern, two more patients probably also had minor changes, one patient had alpha globulinemia, and the fifth patient had hyperglobulinemia, type unknown

Among twenty-seven other myeloma patients in whom either beta or gamma globulin was increased, or in whom only minor anomalies of the globulins were found, no plasma cell leukemia was observed

In this connection it may be of some interest to analyze the data of thirteen patients who, at autopsy, showed infiltration of the visceral organs with myeloma cells, without invasion of the peripheral blood. In five of the thirteen cases electrophoretic patterns were made Only one case had minor anomalies, one had a beta pattern, and three had gamma patterns (table 6)

Wuhrmann, Wunderly, and Hugentobler[217] report that in Switzerland a correlation between the cell types and the particular electrophoretic pattern seems to exist. Their cases with predominant

it seems worthwhile to record briefly the clinical details of three patients whom we have observed (table 5).

was found She was severely anemic and Bence Jones protein was found in the urine The serum albumin was 3 2 Gm per cent, the serum globulin 5 Gm. per cent Bone marrow smears showed the characteristic picture of multiple myeloma Roentgen examination revealed a large expanding soap-bubble like lesion in the left humerus (fig 11) and many translucent osteolytic areas in the rest of the skeleton The patient died after four months in the hospital and at autopsy myelomatous involvement and fractures of many bones were found In addition, parenchymatous degeneration of heart, liver, and kidneys, and a chronic peptic ulcer of the duodenum were present

The second patient with alpha globulinemia was admitted with the diagnosis of multiple myeloma, made in another hospital after bone x-rays and sternal marrow aspiration had been performed She had generalized bone pains and moderate anemia The urine contained 3 plus albumin, but no Bence Jones protein The blood pressure was 170/100 The phenolsulphonphthalein test showed 20 per cent excretion in the first hour and 5 per cent in the second hour The blood urea nitrogen was determined three times and reported as 12, 19, and 26 mg per cent respectively Serum albumin was 5 5 per cent, serum globulin, 2 2 Gm per cent Bone marrow smear was typical for myeloma She was treated with twenty-one injections of stilbamidine which resulted in some relief of bone pain

She was readmitted four months later Bence Jones protein was now found in the urine The blood pressure was 164/100, and azotemia was now present. At this time the serum albumin was found to be 5 4 Gm per cent, the serum globulin 3 1 Gm per cent Notwithstanding the normal serum globulin as determined by the Howe method, the electrophoretic pattern showed the presence of a sharp alpha-2 peak which contained 28 2 per cent of the total serum protein The phenolsulphonphthalein excretion in two hours amounted to 11 per cent

In the course of the next four months she developed severe anemia and increasing renal insufficiency The blood pressure rose to 180/95 She was subsequently admitted to another hospital where she ultimately died in uremia

Shortly before death the serum albumin was found to be 4.4 Gm per cent, the globulin 2 2 Gm per cent. The alpha-2 globulin fraction had come down to normal limits, but the beta globulin fraction was now slightly increased to 19 per cent

At no time during the observation did she have any marked degree of hyperglobulinemia or hyperproteinemia Although at one time this patient had an excess of alpha-2 globulin, she did not have the marked alpha globulinemia which the other two patients presented

The third patient was first diagnosed as a myeloma case in 1945. At that

(table 7, case 2a, case 5) the albumin content was so low that the total protein was only slightly, if at all, increased. In case 2 the beta globulins increased considerably in the course of six months from 32 to 71 per cent of the total protein During the same period the condition of the patient deteriorated rapidly

Case 1 was treated with 274 Gm of urethane between June 22 and October 12, 1949. Under influence of this drug, the total protein decreased considerably—from 10.9 to 7.1 Gm However, remarkably enough, despite this drop the relative percentage of albumin, alpha globulin, and beta globulin did not change This agrees with the experience of Effersoe and his collaborators[53] who found that under ACTH treatment the total protein of the serum decreases but the relative percentage of the different globulins as determined by electrophoretic analysis does not change. The course of these six cases did not differ from the general pattern Only case 5 lived longer than the average patient in this series.

Case 6 was interesting in that he was admitted as a case of solitary myeloma but soon developed a generalization of the disease process All cases with increased beta globulin had a marked decrease of the albumin fraction, with the exception of case 2 in the initial stages of the disease Six months before death, the serum albumin content of this patient was still normal (56 per cent), but the beta globulin had already increased to 32 per cent of the total protein Six months later,

TABLE 7 —*Findings in Six Patients with Beta Patterns on Electrophoresis of Serum*

	Date	Name	Albumin	Alpha-1	Alpha-2	Beta	Gamma	Urine B J	Total protein or alb /glob (Gm per cent)
			(Per cent of total serum protein)						
1a.	6/29/49	Sp	25 99	2 6	6 5	64 9	—	Neg	1/5/9 4
1b	11/17/49	Sp	29 89	15 66		54 44		Neg	2 5/4 6
2a	5/6/48	Ta	55 9	7 7	4 4	32 0	—	Neg	2 3/5 8
2b	11/21/48	Ta	25 73	3 34	0	70 93		Neg	2 7/10 1
3a	7/9/49	De	14 5	3 5	7 2	74 9	—	Neg	1 5/7 1
3b	11/10/49	De	25 6	9 9		64 6		Neg	1 5/8 9
4	1/12/48	Sn	21 5	2 0	4 1	72 4		+ +	2 2/8 0
5a	6/26/49	Go	37 9	4 8	8 0	49 3		Neg	2 9/4 4
5b	7/26/49	Go	34 9	3 4	4 6	53 4		Neg	T P 8 65
5c	8/6/49	Go	30 9	6 5	9 0	49 5		Neg	T P 7 80
6	10/23/47	Sh	Plate broke					+ +	

TABLE 6 —*Electrophoretic Patterns Made in Five Cases of Multiple Myeloma with Visceral Infiltration but without Invasion of Peripheral Blood by Myeloma Cells*

Case	Urinary Bence Jones	Electrophoretic abnormalities	Alb /glob	Sites of myeloma infiltration
St	4 plus	Alpha 19 2%	4 1/1 6	Liver, spleen, kidneys, lymph nodes, peritoneum, pleura
De	Neg	Beta 65%	1 5/8 9	Left kidney
Alp	Neg	Gamma 61 3%	2 5/7 9	Liver, spleen, kidney
CO	Positive	Gamma 89 1%	2 4/8 3	Spleen, retroperitoneal lymph nodes
Co	Neg	Gamma 60 2%	3 0/8 7	Spleen, liver

increase in the alpha globulins had the most immature type of myeloma cells, consisting mainly of young plasmoblasts with nuclei resembling those of reticulum cells This group ran the most malignant course Those cases in which a predominant increase in gamma globulins was found, had more mature myeloma cells with a typical nucleus and nucleolus and the disease process progressed much more slowly Cases with an increase in the beta globulins were intermediate between the two extremes Olhagen and his colleagues[136a] concluded that in beta and gamma globulinemia the myeloma cells had the character of plasmoblasts, in cases with Bence Jones proteinuria, the myeloma cells were myeloblastic in character On the other hand, Janssen and his associates[88] did not find any correlation between the results of the electrophoretic fractionation of the serum and the prevalent type of myeloma cells. An analysis of our cases with increased alpha globulins also failed to confirm any correlation with a specific cell type. The clinical course of these three cases was not significantly different from other cases of multiple myeloma The myeloma cells of the three patients with alpha-2 globulinemia did not differ in any way from the average On the contrary, there were perhaps even fewer myeloma cells of the reticulum cell type in the bone marrow of these three patients than in many other cases of myeloma which were studied.

The observation of the patient with combined alpha-1 and alpha-2 globulinemia presents several different problems which will be discussed on page 94.

Beta patterns The six myeloma cases who showed a beta pattern on electrophoresis of the serum all had a more or less marked hyperproteinemia. They all had hyperglobulinemia, but in some cases

TABLE 8—*Findings in twenty-one Patients with Gamma Patterns on Electrophoresis of Serum*

	Date	Name	Albumin	Alpha-1	Alpha-2	Beta	Gamma	Urine B J	Total protein or alb /glob (Gm per cent)
			(Per cent of total serum protein)						
1a.	5/14/48	Re	37 1	6 0	11 5	9 8	35 6	++	3 8/4 7
1b	9/28/48	Re	29 7	1 4	5 5	5 5	58 0	++	T P 10 8
2	4/26/48	Br	22 7	3 4	7 2	7 2	59 4	Neg	2 4/7 1
3	12/18/47	Co	28 2	5 2	6 7	8 4	51 4	Neg later +	2 6/7 6
4	6/7/48	Bl	21 9	2 2	5 7	8 1	62 1	Neg later +	2 4/7 6
5	8/18/49	Lo	19 6	1 4	2 2	2 7	74 1	Neg	2 9/8 8
6	6/28/49	Re	24 9	1 7	5 5	1 7	66 3	Neg	1 8/9 3
7	10/14/47	H Co	6 1	1 6	1 6	1 0	89 1	++	1 7/11 34
8	3/24/49	H Co	26 76	4 13	6 42	8 56	54 3	Neg	3 6/6 1
9	3/2/49	Ho	30 4	2 5	4 2	4 13	58 7	Neg	3 2/7 3
10	7/9/47	Ka	20 4	4 8	5 4	7 3	62 0	Neg.	1 9/7 3
11	3/2/49	Le	17 3	2 1		0	80 6	Neg	12 7 T P
12a	6/15/50	Le	19 3	3 7	12 9		64 2	Neg	2 3/8 5
12b	7/13/50	Le	21 4	2 6	2 5	4 0	69 45	Neg	2 6/5 8
13	5/14/47	Ne					70 1	Neg	3 4/11 8
14	8/10/50	Pa	25 08	3 37	6 4	6 19	58 9	Neg	2 5/7 0
15	7/8/47	Th	34 7		5 3	11 0	49 4	Neg	3 4/6 5
16	7/12/48	Ra	20 8		4 0	5 4	69 8	Neg	2 4/6 5
16a	4/26/49	Ra	16 5	3 2	2 4	7 0	70 9	Neg	1 9/9 3
17	6/2/50	Gu	34 9	5 1	6 7	7 27	46 0	Neg	2 2/5 4
18a	6/6/49	Ma	7 2	1 0	3 0		88 8	Neg	1 5/11 2
18b	6/13/49	Ma	9 4	0 9	1 1	1 1	87 6	Neg	T P 12–2
18c	6/18/49	Ma	6 3	0 7	1 3	1 2	90 5	Neg	T P 13 0
19a	10/16/47	Ph Co	20 6		4 6	3 8	71 0	Neg	2 2/8 8
19b	10/30/47	Ph Co	20 1	1 1	1 7	3 9	70 33	Neg	T P 11 8
19c	2/14/50	Ph Co	20 6	2 4	7 3	6 94	62 71	Neg	T P 10 0
19d	3/18/50	Ph Co	23 5	3 6	5 4	6 96	60 19	Neg	T P 12 2
20	5/29/48	Ve	40 7	5 4	6 9	10 1	37 2	Neg	4 3/4 7
20a	6/27/49	Ve	25 9	1 6	7 1	7 9	57 6	Neg	2 6/7 5
20b	10/12/49	Ve	20 96	5 2	2 96	16 1	54 97	Neg	2 2/8
20c	5/1/50	Ve	28 6	4 2	5 4	9 5	52 4	Neg	T P 8 6
20d	11/28/50	Ve	28 1	3 9	4 6	7 3	56 2	Neg	T P 9 3
21	9/22/48	Al	24 2	4 0	4 4	6 0	61 3	Neg	2 5/7 9

3 All values exceeding the maximal normal beta globulin content of the serum (15.1 per cent), were considered abnormal.

4 All values exceeding the maximal normal gamma globulin content of the serum (16.8 per cent) were considered abnormal.

It will be seen that the three patients (table 9, 1b, 8, 9) with slight increase of the alpha-1 globulin fraction varied between 9 2 and 11 2 per cent The eight patients with minor increase of the alpha-2 frac-

shortly before death, the albumin content had decreased to 25.7 per cent, while the beta globulin content had increased to 71 per cent.

Of the six patients with beta globulin patterns, only two had Bence Jones protein in the urine. Throughout their period of observation, the four other patients never had Bence Jones proteinuria. In five of the six cases the gamma globulin was very small indeed. In the sixth case the complete analytical data are not available, although it is known that this patient had a beta globulin pattern.

Gamma patterns All patients with a high gamma globulin of the serum had a decreased serum albumin. In case 20 (table 8), however, a low normal serum albumin of 40 7 per cent was found when she was first admitted. Two years later the albumin content had decreased to 25 9 per cent, while the gamma globulin had increased to 57 6 per cent. These percentages remained about the same for the next eighteen months. In all patients with a high gamma globulin the Howe fractionation also showed the existence of hyperglobulinemia. In case 1 the total protein increased in four months from 8.5 Gm. to 10 8 Gm At the same time the gamma globulin increased from 35 6 per cent to 58 per cent, and the albumin decreased from 37 per cent to 29.7 per cent. In case 16 the total protein increased in the course of nine months from 10.6 Gm. to 12 Gm Here, however, the relation between the different fractions remained remarkably constant in the course of two and a half years In case 17 no change occurred in the course of nine and a half months. Case 12 received 2 Gm. of urethane daily between June 15, 1950 and July 8, 1950. During this period the total protein of the serum decreased from 10 8 to 8 4 Gm. per cent, but the relative proportion of the different globulin fractions did not change, just as was noted in a patient with a beta globulin peak (table 7, case 1).

Minor anomalies There were thirteen patients with minor anomalies on electrophoretic analysis of the serum The differentiation of a normal electrophoretic pattern from a pattern with minor anomalies and also the distinction between minor anomalies and actual alpha, beta, and gamma patterns, is completely arbitrary. We have set up the following criteria:

1. All values exceeding the maximal normal alpha-1 globulin content of the serum (8.4 per cent) were considered abnormal.
2. All values exceeding the maximal normal alpha-2 globulin content of the serum (10.2 per cent) were considered abnormal.

TABLE 8—*Findings in twenty-one Patients with Gamma Patterns on Electrophoresis of Serum*

	Date	Name	Albumin	Alpha-1	Alpha-2	Beta	Gamma	Urine B J	Total protein or alb /glob (Gm per cent)
			(Per cent of total serum protein)						
1a	5/14/48	Re	37 1	6 0	11 5	9 8	35 6	++	3 8/4 7
1b	9/28/48	Re	29 7	1 4	5 5	5 5	58 0	++	T P 10 8
2	4/26/48	Br	22 7	3 4	7 2	7 2	59 4	Neg	2 4/7 1
3	12/18/47	Co	28 2	5 2	6 7	8 4	51 4	Neg later +	2 6/7 6
4	6/7/48	Bl	21 9	2 2	5 7	8 1	62 1	Neg later +	2 4/7 6
5	8/18/49	Lo	19 6	1 4	2 2	2 7	74 1	Neg	2 9/8 8
6	6/28/49	Re	24 9	1 7	5 5	1 7	66 3	Neg	1 8/9 3
7	10/14/47	H Co	6 1	1 6	1 6	1 0	89 1	++	1 7/11 34
8	3/24/49	H Co	26 76	4 13	6 42	8 56	54 3	Neg	3 6/6 1
9	3/2/49	Ho	30 4	2 5	4 2	4 13	58 7	Neg	3 2/7 3
10	7/9/47	Ka	20 4	4 8	5 4	7 3	62 0	Neg	1 9/7 3
11	3/2/49	Le	17 3	2 1		0	80 6	Neg	12 7 T P
12a	6/15/50	Le	19 3	3 7	12 9		64 2	Neg	2 3/8 5
12b	7/13/50	Le	21 4	2 6	2 5	4 0	69 45	Neg	2 6/5 8
13	5/14/47	Ne					70 1	Neg	3 4/11 8
14	8/10/50	Pa	25 08	3 37	6 4	6 19	58 9	Neg	2 5/7 0
15	7/8/47	Th	34 7		5 3	11 0	49 4	Neg	3 4/6 5
16	7/12/48	Ra	20 8		4 0	5 4	69 8	Neg	2 4/6 5
16a	4/26/49	Ra	16 5	3 2	2 4	7 0	70 9	Neg	1 9/9 3
17	6/2/50	Gu	34 9	5 1	6 7	7 27	46 0	Neg	2 2/5 4
18a	6/6/49	Ma	7 2	1 0	3 0		88 8	Neg	1 5/11 2
18b	6/13/49	Ma	9 4	0 9	1 1	1 1	87 6	Neg	T P 12–2
18c	6/18/49	Ma	6 3	0 7	1 3	1 2	90 5	Neg	T P 13 0
19a	10/16/47	Ph Co	20 6		4 6	3 8	71 0	Neg	2 2/8 8
19b	10/30/47	Ph Co	20 1	1 1	1 7	3 9	70 33	Neg	T P 11 8
19c	2/14/50	Ph Co	20 6	2 4	7 3	6 94	62 71	Neg	T P 10 0
19d	3/18/50	Ph Co	23 5	3 6	5 4	6 96	60 19	Neg	T P 12 2
20	5/29/48	Ve	40 7	5 4	6 9	10 1	37 2	Neg	4 3/4 7
20a	6/27/49	Ve	25 9	1 6	7 1	7 9	57 6	Neg	2 6/7 5
20b	10/12/49	Ve	20 96	5 2	2 96	16 1	54 97	Neg	2 2/8
20c	5/1/50	Ve	28 6	4 2	5 4	9 5	52 4	Neg	T P 8 6
20d	11/28/50	Ve	28 1	3 9	4 6	7 3	56 2	Neg	T P 9 3
21	9/22/48	Al	24 2	4 0	4 4	6 0	61 3	Neg	2 5/7 9

3 All values exceeding the maximal normal beta globulin content of the serum (15 1 per cent), were considered abnormal.

4. All values exceeding the maximal normal gamma globulin content of the serum (16 8 per cent) were considered abnormal.

It will be seen that the three patients (table 9, 1b, 8, 9) with slight increase of the alpha-1 globulin fraction varied between 9.2 and 11 2 per cent The eight patients with minor increase of the alpha-2 frac-

shortly before death, the albumin content had decreased to 25.7 per cent, while the beta globulin content had increased to 71 per cent.

Of the six patients with beta globulin patterns, only two had Bence Jones protein in the urine. Throughout their period of observation, the four other patients never had Bence Jones proteinuria. In five of the six cases the gamma globulin was very small indeed. In the sixth case the complete analytical data are not available, although it is known that this patient had a beta globulin pattern.

Gamma patterns All patients with a high gamma globulin of the serum had a decreased serum albumin. In case 20 (table 8), however, a low normal serum albumin of 40.7 per cent was found when she was first admitted Two years later the albumin content had decreased to 25 9 per cent, while the gamma globulin had increased to 57.6 per cent. These percentages remained about the same for the next eighteen months In all patients with a high gamma globulin the Howe fractionation also showed the existence of hyperglobulinemia. In case 1 the total protein increased in four months from 8.5 Gm. to 10.8 Gm. At the same time the gamma globulin increased from 35.6 per cent to 58 per cent, and the albumin decreased from 37 per cent to 29.7 per cent In case 16 the total protein increased in the course of nine months from 10.6 Gm. to 12 Gm Here, however, the relation between the different fractions remained remarkably constant in the course of two and a half years In case 17 no change occurred in the course of nine and a half months. Case 12 received 2 Gm. of urethane daily between June 15, 1950 and July 8, 1950 During this period the total protein of the serum decreased from 10 8 to 8.4 Gm per cent, but the relative proportion of the different globulin fractions did not change, just as was noted in a patient with a beta globulin peak (table 7, case 1).

Minor anomalies There were thirteen patients with minor anomalies on electrophoretic analysis of the serum The differentiation of a normal electrophoretic pattern from a pattern with minor anomalies and also the distinction between minor anomalies and actual alpha, beta, and gamma patterns, is completely arbitrary We have set up the following criteria

1 All values exceeding the maximal normal alpha-1 globulin content of the serum (8.4 per cent) were considered abnormal.

2 All values exceeding the maximal normal alpha-2 globulin content of the serum (10.2 per cent) were considered abnormal.

TABLE 9 —*Findings in Thirteen Patients with Minor Anomalies on Electrophoresis of Serum*

	Date	Name	Albumin	Alpha-1 (Per cent of total serum protein)	Alpha-2	Beta	Gamma		Urine Bence Jones	Alb/glob (Gm per cent)
Normal			56 8 ± 3	7 2 ± 1 2	8 7 ± 1 5	12 8 ± 2 3	14 4 ± 2 4			
1a	6/23/50	Br a	43 85	8 24	*11 45*	11 9	*24 6*	Moderate increase gamma globulin, but without sharp peak Slight decrease albumin	++	
1b	7/10/50	Br b	41 5	*11 2*	*12 2*	10 6	*24 5*		++	2 5/2 9
1c	7/24/50	Br c	51 0	5 6	*11 0*	10 1	*22 34*			3 3/3 4
1d	8/8/50	Br. d	45 8	5 7	*16 7*	6 8	*25 0*	Slight increase alpha-2 peak	++	3 6/3 4
2		Bi	53 3	6 1	3 9	13 6	*23 2*	Moderate increase gamma globulin, but without sharp peak Other fractions normal	++	4 1/2 4
3	6/10/49	He	54 6	5 6	10 6	8 6	*20 6*	Slight increase gamma fraction	++	4 2/2 8
4a	5/23/49	Ro a	52 1	8 3	19 0		*20 5*	Slight increase alpha-2 and gamma fraction		
4b	6/3/49	Ro b	66 7	4 3	*12 4*	3 7	12 9	Slight increase alpha-2 fraction	++	4 2/3 0
5	10/2/47	G	55 6	6 7	*14 6*	14 7	8 6	Slight increase alpha-2 fraction	–	4 9/1 6
6	10/22/48	He	57 6	5 9	*13 24*	11 9	11 35	Slight increase alpha-2 fraction	–	3 8/2 7
7	5/24/50	Hi.	54 9	8 4	*12 5*	10 7	13 5	Slight increase alpha-2 fraction	+++	4 3/1 8
8	10/1/47	S	55 6	*9 2*	9 9	8 0	17 5	Slight increase alpha-2 fraction	+++	4 1/1 6
9	10/18/47	T	55 3	*10 4*	7 8	12 9	15 8	Slight increase alpha-1 fraction	+++	3 9/3 3
10a	2/20/50	C a	53 0	7 45	*12 9*	*20 9*	5 7	Slight increase alpha-2 fraction Moderate increase beta fraction	++	5 9/1 6
10b	9/6/50	C b	58 4	7 17	9 6	7 5	16 8	Normal pattern	++	
11	6/4/48	P Be	59 5	7 5	*12 6*	*17 4*	3 0	Slight increase alpha-2 and beta fraction	–	4 7/2 5
12	12/2/49	La	58 2	8 0	*14 3*	*19 5*	0	Slight increase alpha-2 and beta fraction Hyperproteinemia Diabetes	++	3 9/2 8
13	8/21/47	Za	37 5	5 6	9 7	*16 2*	*19 2*	Slight increase beta and gamma fraction Decreased albumin fraction Diabetes	++	3 9/2 3

tion varied between 11.0 and 16.7 per cent. The four patients with minor anomalies of the beta globulin fraction (table 9, 10a, 11, 12, 13) varied between 19.2 and 25.0 per cent.

The previously quoted observation that there is an inverse relation between hyperglobulinemia and Bence Jones proteinuria in multiple myeloma is confirmed by the findings in our series. Of the thirty-one patients with either alpha, beta, or gamma patterns only seven had Bence Jones proteinuria However, of the thirteen with minor electrophoretic anomalies, all but three had Bence Jones proteinuria The total protein content of the serum of these patients with minor electrophoretic anomalies was within normal limits In two of the thirteen *cases there was a slight increase of the serum globulin In case 1 of* table 9, 3.3 to 3 6 Gm. per cent of albumin and 3.4 Gm. per cent of globulin were found; in case 19 the albumin value was 3 9 Gm. per cent, the globulin value 3 3 Gm per cent The other eleven patients with minor anomalies of the electrophoretic pattern all had normal values as determined by the Howe fractionation One of the thirteen patients (case 10) whose serum was examined twice, had a completely normal electrophoretic pattern on the second examination. In this connection it may be of some importance to report that he did subjectively well on ACTH treatment although the signs of moderate renal insufficiency did not diminish He died suddenly, possibly from a pulmonary embolism. Case 8 whose only anomaly was a very slight increase of the alpha-1 globulin fraction to 9 2 per cent, had multiple myeloma with plasma cell leukemia.

Case 2 had a moderate increase of the gamma globulin fraction to 23 2 per cent. He died in uremia from a typical myeloma kidney. At autopsy he presented, in addition to multiple myeloma, extensive paramyloidosis. The last two patients (cases 12 and 13) have to be given special consideration They not only suffered from myeloma, but also had diabetes. Certain changes of the electrophoretic pattern may well have been related to the diabetes and not to the myeloma

As shown by the four electrophoretic analyses performed on the first patient, even these minor anomalies follow a special pattern. This patient always had a slight increase of the alpha-2 fraction and a moderate increase of the gamma globulin.

Janssen[88] found a marked decrease of the gamma fraction in all patients who showed only minor anomalies Two of our patients (1 and 2) had, however, a moderate increase of the gamma globulin

usually completely absent Waldenström and Pederson[201] found no case of macroglobulinemia among their twenty-seven cases of myeloma However, among their cases of "macroglobulinemia" (p 19) several cases were so similar to myeloma that they could be distinguished only by the presence of the macroglobulins found on ultracentrifugation It may be that this distinction is somewhat arbitrary.

Paramyloidosis

One of the more fascinating aspects of the study of multiple myeloma is its peculiar relationship to systematized amyloidosis or paramyloidosis Adams and Dowse[3] first drew attention to this association in 1872 Goltz[68b] in his review article, mentions that these authors did not actually recognize the presence of amyloid in their patient and that Askanazy, in 1904, was the first to describe correctly the occurrence of amyloid in multiple myeloma. Magnus-Levy[117,118] has championed the idea that Bence Jones protein is chemically related to amyloid Nearly all patients with myeloma and amyloid have Bence Jones proteinuria Magnus-Levy discusses the possibility that the deposition of amyloid might be a reaction of the tissues to the abnormal globulins present in multiple myeloma He believes that the myeloma cell produces amyloid just as it manufactures the other abnormal proteins He cites an interesting observation in which amyloid was found in myeloma cells obtained by sternal marrow puncture Since myeloma cells are not phagocytic in nature, this finding, of course, would indicate that amyloid could very well be manufactured by myeloma cells Trubowitz[195a] found amyloid, not only in myeloma cells, but also in the polynuclear leukocytes obtained by bone marrow puncture. In his opinion the amyloid was not formed in the cells but ingested by them As mentioned above this could only hold true for the leukocytes, not for the myeloma cells

Experimental evidence of a possible, but not constant, relationship between amyloid and hyperglobulinemia seems to exist Reimann and Eklund[145] produced amyloidosis in rabbits by injecting sodium caseinate over a period of eight to thirteen months In these rabbits a two to four fold increase of the serum globulin accompanied the amyloidosis These two authors point out that amyloidosis has been produced experimentally by a great variety of substances, including bacterial vaccines, egg albumin, gelatin, peptones, organ transplants, silicates, sulfur, and selenium Kuczynski[96] produced amyloidosis in

Only in four of these thirteen patients (cases 1, 10, 11, 12) was the gamma globulin lower than normal (8.6 per cent, 5.7 per cent, 3 0 per cent, and zero). Wuhrmann[217] has come to the conclusion that patients with minor anomalies of the electrophoretic pattern show a more acute course and have a poorer prognosis than, for instance, the gamma globulin group. This apparently is not the case in our patients, whose period of survival, after the disease was first diagnosed, compared favorably with that of the average myeloma case. The longest period of survival in this group was three years in one case and two years in two other cases

Ultracentrifugation

The introduction of ultracentrifugation has made several important contributions to the study of the abnormal proteins in multiple myeloma It has produced evidence to indicate that some of the unusual patterns obtained with Howe and electrophoretic fractionation of myeloma sera are due to significant Bence Jones proteinemia [70] This is particularly true of those components migrating with the mobility of beta globulin or intermediate between beta and gamma globulins. Bence Jones protein as found in the urine has a fairly uniform sedimentation constant, varying from 2.8 S to 3 7 S, while the abnormal proteins recovered from the blood in different cases have sedimented at a widely different rate.[70,196] Several cases have been reported, however, where Bence Jones proteins with sedimentation constants of 3 0 S and 4.0 S were found in the serum [131]

Determination of the molecular size of the normal serum globulins by ultracentrifugation has demonstrated that the electrophoretic fractions are not homogeneous On the other hand, the abnormal protein of myeloma appears to be an unusually homogeneous globulin constituent of the serum with a sedimentation constant ranging between 6 17 S and 6 76 S [154] Waldenstrom[201] states that no matter whether the increase in plasma protein is due to beta or gamma globulins, it is usually, though not always, accompanied by an increase in that fraction of the plasma proteins with a sedimentation constant of normal globulins, 7 S. This would indicate a molecular weight of approximately 150,000.

Less than 5 per cent of macroglobulins with sedimentation constants of 19 S and 20 S are found in normal sera. This macroglobulin fraction may be increased in other diseases, but in myeloma sera it is

TABLE 10 —*Findings in Eleven Patients with Multiple Myeloma Complicated by Amyloidosis*

Name and age	Site of amyloid	Blood pressure	B U N (mg %)	Alb (Gm %)	Glob (Gm %)	Urine Bence Jones	Bone lesions on x-ray
H O 61 years Male	Spleen, heart, g.i tract, abdominal fat tissue, small arteries of spleen, pancreas, adrenals	144/86	160	4 1	3 9	Positive	Numerous areas of destruction in skull, ischium, and ilium Mild bone pain
M B 45 years Male	Heart, g i tract, spleen, periadrenal fat	115/70	130	4 1	2 4	Positive	No bone lesions No bone pain
A. G. 40 years Male	Extensive involvement of spleen, heart, liver, lymph nodes, kidney, stomach, intestine, bone marrow, conspicuous Russell bodies in marrow	80/60	103	2 6	1 9	Positive	No bone lesions No bone pain
Y B * 52 years Female	Subendocardium, left atrium, myocardium, lung, colon, amyloid tumor of joint capsule of elbow	165/85	40	3 0	2 1	Positive	No bone lesions Severe pain in back
A L 58 years Female	Nodular amyloidosis of small intestine and larynx	170/68	40	3 6	1 3	Positive	Very extensive rarefactions in all bones (including metacarpals) Severe bone pain
A M * 56 years Female	Heart, liver, kidneys, pancreas, g i tract, uterus and ovaries, blood vessel walls	96/66	13	3 2	2 2	Negative	No bone lesions No bone pains
R S 54 years Female	Blood vessel walls of all organs, myocardium, bladder, g i tract	120/70	74	2 5	6 7	Positive	No lytic bone lesions Diffuse demineralization No bone pain
Y S 48 years	Skin, subcutis, tongue, heart, g i tract, skeletal muscle	136/78	36	3 5	2 5	Positive	Universally distributed lytic lesions of skeleton

mice by feeding large amounts of casein. Amyloidosis is frequently found in horses used to produce hyperimmune sera and these animals show a significant increase in the serum globulin level. The localization of the amyloid in these animals resembled the localization of the secondary amyloid found in humans with long standing suppuration.

In recent years, several articles have appeared which point out that hyperglobulinemia, plasmocytosis, and paramyloidosis can all be found as a result of sensitization to drugs[148, 191] or in other disease processes such as trichinosis or systemic lupus erythematosus[191] Marrow puncture in such disease states may reveal 10 to 20 per cent plasma cells, some of which may be binucleated. In such cases the differential diagnosis from multiple myeloma may be difficult. Notwithstanding these superficial similarities, the association of paramyloid with multiple myeloma probably has little in common with such hypersensitivity states. Presently it will be pointed out that in most patients with multiple myeloma in whom paramyloid develops the globulin content of the serum is not increased This is in sharp contrast to the hyperglobulinemia almost invariably found in experimentally produced amyloid or the amyloidosis associated with hypersensitization

Paramyloidosis in multiple myeloma must be identified with primary amyloidosis In the secondary amyloidosis which follows prolonged suppuration, the localization of the amyloid is predominantly in the liver, spleen, kidneys, adrenals, and blood vessel walls In primary amyloidosis or paramyloidosis, the deposition occurs in atypical locations, mainly in the mesodermal tissues of the heart, blood vessels, and gastrointestinal tract. Paramyloid is also found in many other organs[13, 42 105] but only rarely in the parenchyma of the liver, kidneys, adrenals, or spleen Involvement of blood vessel walls is common, both in secondary amyloidosis and in paramyloidosis. The formation of amyloid tumors is seen only in paramyloidosis Although exceptions must exist, it can be stated, as a general rule, that suppuration does not lead to paramyloidosis and that multiple myeloma does not give rise to true amyloidosis.

There are considerable differences in the staining characteristics of true or secondary amyloid and paramyloid; secondary amyloid takes up congo red and the metachromatic dyes more avidly than paramyloid These variations in response to different staining methods indicate that chemical differences must exist between paramyloid and

TABLE 10.—*Findings in Eleven Patients with Multiple Myeloma Complicated by Amyloidosis*

Name and age	Site of amyloid	Blood pressure	B.U.N (mg %)	Alb (Gm. %)	Glob (Gm %)	Urine Bence Jones	Bone lesions on x-ray
H O 61 years Male	Spleen, heart, g i tract, abdominal fat tissue, small arteries of spleen, pancreas, adrenals	144/86	160	4 1	3 9	Positive	Numerous areas of destruction in skull, ischium, and ilium Mild bone pain
M B 45 years Male	Heart, g i tract, spleen, periadrenal fat	115/70	130	4 1	2 4	Positive	No bone lesions No bone pain
A G. 40 years Male	Extensive involvement of spleen, heart, liver, lymph nodes, kidney, stomach, intestine, bone marrow, conspicuous Russell bodies in marrow	80/60	103	2 6	1 9	Positive	No bone lesions No bone pain
Y B * 52 years Female	Subendocardium, left atrium, myocardium, lung, colon, amyloid tumor of joint capsule of elbow	165/85	40	3 0	2 1	Positive	No bone lesions Severe pain in back
A L 58 years Female	Nodular amyloidosis of small intestine and larynx	170/68	40	3 6	1 3	Positive	Very extensive rarefactions in all bones (including metacarpals) Severe bone pain
A M * 56 years Female	Heart, liver, kidneys, pancreas, g i. tract, uterus and ovaries, blood vessel walls	96/66	13	3 2	2 2	Negative	No bone lesions No bone pains
R. S 54 years Female	Blood vessel walls of all organs, myocardium, bladder, g i. tract	120/70	74	2 5	6 7	Positive	No lytic bone lesions Diffuse demineralization No bone pain
Y. S 48 years	Skin, subcutis, tongue, heart, g i tract, skeletal muscle	136/78	36	3 5	2.5	Positive	Universally distributed lytic lesions of skeleton

TABLE 10.—*Findings in Eleven Patients with Multiple Myeloma Complicated by Amyloidosis.*—(*Continued*)

Name and age	Site of amyloid	Blood pressure	B U N (mg %)	Alb (Gm %)	Glob (Gm %)	Urine Bence Jones	Bone lesions on x-ray
E B 58 years	Tongue, striated muscle, joint capsules, skin	136/78	28	3 3	2 5	Positive	Extensive lytic lesions of spine, forearms, humeri, femur
I P 39 years	Tongue, sterno-clavicular joint (No autopsy)	120/68	16	2 6	5 0	Positive	Many destructive lesions of long bone, skull, pelvis, and phalanges
K B 49 years	Tongue, joint capsules, nodes, skin (No autopsy)	110/60	17	3 7	2 0	Positive	Extensive areas of destruction, plus severe generalized demineralization

The first eight patients were autopsied at the Mount Sinai Hospital, the ninth patient was autopsied elsewhere In the last two cases the diagnosis was made by biopsy
* Reported by Wallerstein, R S [204]

true amyloid As a matter of fact, although both substances appear to be protein-carbohydrate complexes, the solubility of paramyloid differs greatly from true amyloid (Hass, Huntington, and Krumdieck[75a]) There are conflicting opinions as to whether or not amyloid consists of a protein-chondroitin-sulfuric acid compound.

In this series, eight cases of paramyloidosis were found among forty-one cases of multiple myeloma which came to autopsy (table 10). Three other cases of paramyloidosis were seen. Two of these were confirmed by biopsy and another was autopsied at another hospital. The localization of the paramyloid in these cases, with a few exceptions, duplicated that of primary systemic amyloidosis since the amyloid was found to be deposited in atypical locations in the mesenchymal tissues (figs. 32–35) All but one of the eight autopsied cases were found to have amyloid involvement of the gastrointestinal tract Single instances of deposits of paramyloid were found in the subcutis, lymph nodes, pancreas, uterus, ovaries, fat tissue, lung, joint capsules, and larynx (fig 33). Only two of the eight autopsied cases had, in addition, amyloid deposition in the liver, spleen, or kidneys. None of these cases exhibited amyloid of the adrenals. Involvement of the



FIG 32 —(*a*) Masses of dark staining paramyloid infiltrating the auricular endocardium (*b*) Paramyloid in the walls of the arteries of the tongue (*c*) Blood vessel walls of gingiva thickened by paramyloid

joint capsules and voluntary muscles, as pointed by Tarr and Ferris,[190] may produce a picture closely resembling rheumatoid arthritis (fig 35) Five of the eight autopsied cases demonstrated paramyloid infiltration of the heart and four of these patients died in severe congestive heart failure. In the literature, one can find several cases of heart

failure of "unknown origin" occurring in patients who had no signs or symptoms of skeletal involvement during life. In these cases the autopsy revealed the presence of paramyloidosis of the myocardium, and only after a careful examination of the bone marrow was the correct diagnosis of multiple myeloma made. The possibility that

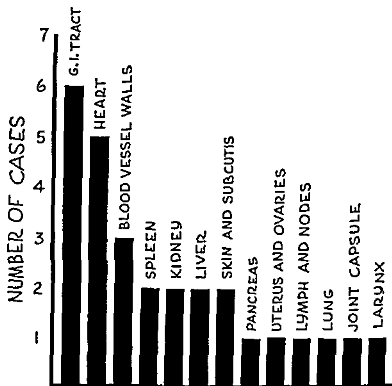


FIG 33 —Distribution of paramyloidosis found in eight autopsied cases of multiple myeloma.

amyloid of the cutaneous blood vessels may be the cause of unexplained purpura has been discussed before (p. 19).

One of the cases of paramyloidosis in myeloma studied at this hospital, but autopsied elsewhere, was the only case to demonstrate macroglossia due to paramyloid deposition [178] Enlargement of the tongue is a prominent feature in many cases of paramyloidosis reported by other authors. In two other patients we noted the development of small tumors on the tongue (fig. 34) and the mucous membrane of the mouth, which at biopsy were found to consist of amyloid.

One patient with myeloma, in whom no grossly visible lesions could be detected in the tongue or mucous membrane of the mouth, had a biopsy of the gingiva done during life as recommended by Selikoff[167] Extensive amyloid infiltration of the submucous layers and especially of muscular coats of the blood vessels were found (fig. 36). At autopsy of this case, there was widespread paramyloidosis



FIG 34 —Nodular infiltration of tongue with amyloid in multiple myeloma

involving the heart (fig 32a), intestine, and subcutis, and virtually all of the smaller arteries of the viscera Interestingly enough, this woman had almost total alopecia due to amyloid infiltration of the subcutaneous tissue of the scalp Another patient had extensive hard subcutaneous tumors consisting of amyloid, which could be palpated as large plaques below the breasts and all over the abdominal wall. Paige,[135a] in 1931, described a comparable case

Four of the eight autopsied cases with paramyloidosis died in uremia Three of these cases had myeloma kidneys without renal

failure of "unknown origin" occurring in patients who had no signs or symptoms of skeletal involvement during life. In these cases the autopsy revealed the presence of paramyloidosis of the myocardium, and only after a careful examination of the bone marrow was the correct diagnosis of multiple myeloma made. The possibility that

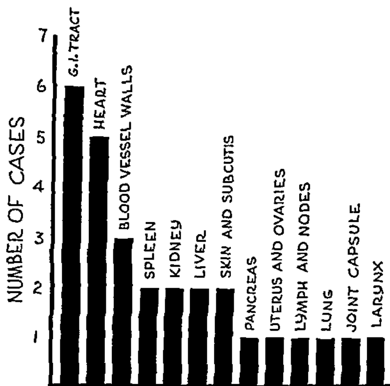


FIG 33.—Distribution of paramyloidosis found in eight autopsied cases of multiple myeloma.

amyloid of the cutaneous blood vessels may be the cause of unexplained purpura has been discussed before (p 19).

One of the cases of paramyloidosis in myeloma studied at this hospital, but autopsied elsewhere, was the only case to demonstrate macroglossia due to paramyloid deposition.[178] Enlargement of the tongue is a prominent feature in many cases of paramyloidosis reported by other authors. In two other patients we noted the development of small tumors on the tongue (fig. 34) and the mucous membrane of the mouth, which at biopsy were found to consist of amyloid.

the third 5.0 Gm. per cent. To explain this phenomenon, Apitz[3] has suggested that instead of circulating in the blood, the abnormal globulins are deposited in the tissue as paramyloid.

An interesting feature in this group of patients with paramyloidosis, secondary to multiple myeloma, is the relative rarity of bone lesions on x-ray examination. Five of eleven patients with paramyloidosis had no recognizable areas of bone destruction, which are so characteristic of myeloma and only one of these five had significant bone pains. This feature emphasizes again the difficulty which may arise in the diagnosis of this type of case As Apitz[3] and later Lichtenstein and Jaffe[105] have stressed, any case of paramyloidosis should be investigated very carefully for multiple myeloma Apitz even goes so far as to state that all cases of paramyloidosis are due to myelomatosis and that in those cases of paramyloidosis, where careful examination does not reveal the presence of myelomatosis, the latter will develop if the patient lives long enough

The following is a case history of a patient with amyloidosis, marked lymphadenopathy, and hepatosplenomegaly, who presented a bizarre picture of anasarca, uremia, congestive failure, and gastrointestinal bleeding

This 42 year old white male entered the hospital complaining of massive, repeated tarry and bloody bowel movements for six months One month before admission to the Mount Sinai Hospital he developed edema extending from the feet to the thighs, swelling of the abdomen, and paroxysmal nocturnal dyspnea

On admission to this hospital the patient was acutely ill, pale and orthopenic Petechiae were noted in the conjunctival sacs, on the palate, and in the buccal mucosa The tongue was smooth with marginal ulcerations but was not enlarged Neck veins were markedly distended and filled from below The heart sounds were of poor quality, but no murmurs were heard There were signs of bilateral pleural effusions There were numerous rubbery, movable, 2 to 5 cm lymph nodes in the cervical, axillary, and inguinal regions The spleen was huge It was smooth and stony hard and extended to the pelvic brim inferiorly and to the umbilicus medially The liver edge was felt five centimeters below the right costal margin There was 4 plus pitting sacral, scrotal, and leg edema

Laboratory examination revealed a severe hypochromic anemia with 8 5 Gm of hemoglobin and 3,000,000 red blood cells per cu mm The white blood cell count was 21,000 per cu mm with a normal differential Platelets numbered 400,000 per cu mm There was 4 plus albuminuria and a positive Jacobson test for Bence Jones protein Blood urea nitrogen on admission was 12 mg per cent The cephalin flocculation and the thymol turbidity were each 1 plus The prothrombin time was 22 5 seconds with a control of 12 seconds Serum

amyloidosis and the fourth had a combination of the two. It would appear, therefore, that when a myeloma patient with amyloidosis develops severe uremia, the renal insufficiency is more likely to be due to a myeloma kidney than to involvement of the kidney by amyloid. Only one of these eight cases had hypertension and this patient did not die in uremia. In this patient the blood urea nitrogen was 40 mg. per cent at death. Of the eleven cases of paramyloidosis in multiple myeloma, which are discussed here, all but one had Bence Jones

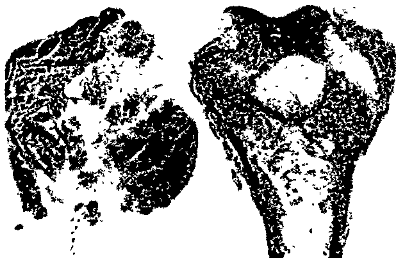


Fig 35 —Large lemon-sized amyloid tumor of joint capsule of elbow in patient with multiple myeloma

proteinuria The frequent combination of Bence Jones proteinuria in paramyloidosis has also been observed by others.[190]

Analysis of the serum globulin levels in myeloma patients with paramyloidosis provides information which conflicts with the observation that in paramyloidosis produced under experimental conditions, hyperglobulinemia is a frequent occurrence Contrary to expectations hyperglobulinemia has been found to be rare in patients with myeloma who develop amyloidosis (Eisen[54a]). This was also the case in our series. In our eleven myeloma patients with paramyloidosis only three had a serum globulin above 2.5 Gm. per cent (table 10). One of these had a serum globulin of 3 9, another of 6 7 Gm per cent and

Calcium and Phosphorus Metabolism

In this laboratory the normal serum calcium varies between 9.5 and 11.5 mg per cent, the normal inorganic phosphorus between 2 and 4 mg per cent and the normal alkaline phosphatase between 4 and 12 King Armstrong units per 100 cc.

Probably as a result of the rapid demineralization of the bones, hypercalcemia and hypercalciuria are common findings in multiple myeloma Gutman and his associates[72] found elevations of the serum calcium above 12 mg. per cent in four of six cases which they studied,

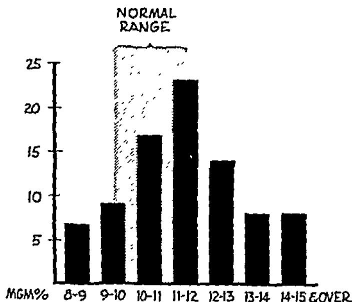


Fig 36 —Distribution of serum calcium levels in multiple myeloma. Note the distinct tendency to hypercalcemia in many of the cases

and found elevations in about 50 to 60 per cent of the cases reported in the literature Bayrd and Heck[11] found only eight of forty-one cases in their series to have serum calcium levels above 12 mg. per cent In our series, thirty of eighty-five cases (34 per cent) in whom the serum calcium was measured, had values above 12 mg. per cent (fig. 36) The highest value recorded was 17 5 mg per cent. Several cases starting with normal serum calcium levels developed elevations later in the course of their illness. It seems, therefore, that high serum cal-

albumin was 2 5 Gm per cent, globulin 1 7 Gm per cent. Electrophoresis revealed the alpha-1 globulin to be increased to 16 8 per cent, the alpha-2 globulin to 25 3 per cent (table 11) *The erythrocyte sedimentation rate was* only 7 mm per hour Twenty-four hour urine protein excretion (Esbach) was 6 2 Gm per liter No bone lesions were demonstrable on skeletal survey. Sternal marrow contained 12 per cent myeloma cells, many of which occurred in clumps

His renal function deteriorated rapidly with the blood urea nitrogen rising to 103 mg per cent PSP test revealed only 25 per cent excretion in two hours. A Congo red test was performed and there was 79 per cent retention in the tissues Three hours after the injection of Congo red, the patient became nauseated, complained of dizziness, went into a state of collapse, and died within a few minutes

Postmortem examination revealed paramyloidosis of the heart, spleen, liver, lymph nodes, gastrointestinal tract, and kidneys The liver weighed 2660 Gm *and the spleen, stained a brilliant orange red by the Congo red given shortly* before death, weighed 1320 Gm The sternal marrow smear, as mentioned above, contained many myeloma cells, the postmortem microscopic sections, however, showed the presence of only a relatively small number of plasma cells The marrow sections, however, contained an unusually large number of intracellular and extracellular bodies, which stained deep blue with Romanofsky stain and pink with hematoxylin and eosin (frontispiece—fig 3e) Many of these were intranuclear, some in the cytoplasm of degenerating cells, and some were apparently lying free in the marrow spaces Because they stained blue with Romanofsky stain, they could not properly be called Russell bodies In addition, they did not have the staining qualities of amyloid.

The use of the Congo red test for the diagnosis of amyloid is of little *value in the case of paramyloidosis for several reasons* Since in paramyloidosis the liver is commonly spared, the mass of amyloid tissue *which is present in the body is usually too small to produce a sig*nificant retention of the dye In addition, paramyloid takes up Congo red less avidly than does true amyloid. If, however, paramyloid of the

TABLE 11 —*Atypical Alpha Pattern Found on Electrophoresis of Serum of Patient with Multiple Myeloma and Amyloidosis*

Date	Name	Albumin	Alpha-1	Alpha-2	Beta	Gamma		B J Urine	Alb /Glob Gm per cent
		(Per cent of total serum protein)							
7/27/50	Go	40 8	16 85	25 34	10 14	7 12	Marked increase alpha-1 and alpha-2 globulin but without sharp peak Decreased albumin and total protein content	++	2 5/1 7

tongue, buccal mucosa, or skin is suspected, then Congo red can be used for the diagnosis. After local injection of this dye, the amyloid tumors assume a fiery red color.

Calcium and Phosphorus Metabolism

In this laboratory the normal serum calcium varies between 9.5 and 11.5 mg. per cent, the normal inorganic phosphorus between 2 and 4 mg. per cent and the normal alkaline phosphatase between 4 and 12 King Armstrong units per 100 cc

Probably as a result of the rapid demineralization of the bones, hypercalcemia and hypercalciuria are common *findings in multiple* myeloma Gutman and his associates[72] found elevations of the serum calcium above 12 mg. per cent in four of six cases which they studied,

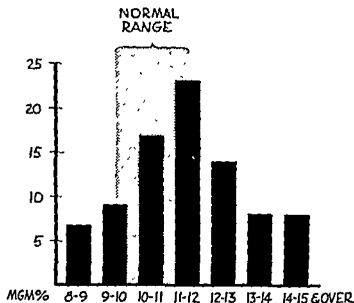


Fig 36 —Distribution of serum calcium levels in multiple myeloma Note the distinct tendency to hypercalcemia in many of the cases.

and found elevations in about 50 to 60 per cent of the cases reported in the literature Bayrd and Heck[19] found only eight of forty-one cases in their series to have serum calcium levels above 12 mg. per cent. In our series, thirty of eighty-five cases (34 per cent) in whom the serum calcium was measured, had values above 12 mg. per cent (fig. 36) The highest value recorded was 17.5 mg. per cent Several cases starting with normal serum calcium levels developed elevations later in the course of their illness. It seems, therefore, that high serum cal-

cium indicates advanced or rapidly spreading disease and is often a poor prognostic sign. Patients with severe uremia complicating multiple myeloma, generally had normal or even low serum calcium levels. Of the seven cases in this series with serum calcium below 9 mg. per cent, five were in uremia.

The alkaline phosphatase is usually normal in multiple myeloma, although Adams, Alling, and Lawrence[1] reported an elevation above normal in 48 per cent of their cases. In our series, seventy-one of eighty-six patients (83 per cent) had repeated values within normal limits The other patients, most of whom had large fractures, had elevations at one time or another. Only five patients had serum alkaline phosphatase levels of more than 16 King-Armstrong units, but two of these had normal values on subsequent determinations, and a third had cirrhosis of the liver Although rare exceptions exist as noted, when the serum alkaline phosphatase remains elevated in the absence of a gross pathologic fracture or of liver disease, the diagnosis of multiple myeloma should be questioned

The great majority of cases had no alteration of the serum phosphorus levels except in the presence of uremia, where it was generally elevated In none of the cases in the entire series was the metabolic triad of hypercalcemia, hypophosphatemia, and elevated serum alkaline phosphatase present. This would seem to provide a sound differential diagnostic point between hyperparathyroidism and multiple myeloma

Of the forty-one autopsied cases, metastatic calcification was found in five Four of these had renal calculi and the fifth had microscopic calcifications in the lungs. In one of the autopsied cases, minimal hyperplasia of the four parathyroid glands was found in addition to undoubted myeloma This patient died with myeloma kidneys, a blood urea nitrogen of 69 mg per cent, and a creatinine of 6 4 mg per cent The serum calcium was 16.8 mg per cent, the serum phosphorus 1 0 mg per cent, and the alkaline phosphatase 9 King-Armstrong units The patient had been on a high calcium and vitamin D intake while at home

Uric Acid Metabolism

Another common biochemical abnormality noted in multiple myeloma is a significant elevation of the serum uric acid level, even in the absence of renal insufficiency. The uric acid level was above

4 mg. per cent in fifty-four (87 per cent) of the sixty-two cases in which determinations were made. In 50 per cent of the cases tested it was above 7 mg. per cent This elevation of the uric acid, first described by Stewart and Parkes-Weber[188] is evidently due to the increased catabolism of nucleoproteins derived from the nuclei of myeloma cells

7. SOLITARY MYELOMA

Multiple myeloma is a generalized disease of the skeleton. Even in the absence of x-ray changes in the bones, bone marrow aspiration usually reveals the presence of myeloma cells, wherever it is made. A single focus of myelomatous tissue, without dissemination to the rest of the skeleton, has been termed "solitary myeloma" or "solitary plasmocytoma" The literature contains many such case reports, but in the majority of these, the follow-up data are not adequate to rule out subsequent generalization of the disease The roentgenographic picture of a solitary myeloma has been described carefully by Paul and Pohle [139] They stressed the very important point that solitary myeloma usually presents the roentgen appearance of either a giant cell tumor or a destructive bone lesion, nearly always localized in the intramedullary cavity. The roentgenologic similarity of a solitary plasmocytoma and a giant cell tumor is of great importance and has already been emphasized. Since giant cell tumors occur only rarely in flat bones, an osteolytic lesion showing the presence of many septa and localized in a flat bone is more likely to be a solitary myeloma. Most of the solitary myelomas are localized in one of the pelvic bones or in the spine. The frequency of solitary myeloma as a cause for extradural compression of the spinal cord has been mentioned above (p 32).

Bichel and Kirketerp[25] reviewed the literature on solitary myeloma up to 1938. They laid down rigid criteria for the diagnosis, and accepted only two cases as proven. Before considering the diagnosis of solitary myeloma, its presence should be established by biopsy A skeletal survey should eliminate the presence of other radiologic lesions. The sternal marrow puncture should be negative. As a rule, hyperglobulinemia and Bence Jones proteinuria should be absent.

However, slight changes in the electrophoretic pattern may be present (p 100) Bence Jones proteinuria has been described in cases of solitary myeloma which were confirmed at autopsy.[114] This must be a rare occurrence and in our material the appearance of Bence Jones proteinuria is a prognostic sign predicting early spread of the disease. Finally, no generalization of the myelomatous process should occur during a long period of observation. According to these criteria, Bichel and Kirketerp accepted only two of twenty-seven cases reported in the literature as solitary myeloma. Tennent,[192] in 1945, accepted only twenty of fifty cases reported Lumb and Prosser[114] found eighteen proved cases, six of which were located in the femur, four in the vertebral column, four in the pelvic bones other than the sacrum, two in the humerus, one in the tibia, and one in the skull Aufses,[14] in 1948, described a case of solitary myeloma in the rib observed in the Mount Sinai Hospital, which was followed for three years without any spread, and he collected ten additional cases, reported after 1938, which were followed for three years or more without generalization.

Christopherson and Miller,[35] in 1950, collected all the cases of solitary plasma cell myeloma of bone they could find in the literature They tabulated the cases and arranged them into three groups

1. There were twenty-two cases which had been followed for at least three years without signs of generalized dissemination To this group they added three cases of their own Most of the cases in this category were followed for a period of more than four years; five cases were even followed for a period of more than ten years

2. There were twelve cases in which a solitary myeloma was found at autopsy It is evident that in most of the cases of the latter group the period of observation was quite short, varying between a few days and one year It is, of course, impossible to determine whether or not, in any of these cases, dissemination might have occurred at a later date if the patient had lived longer.

3 There were fifteen cases which had been followed for a period varying between one and three years It is also difficult to evaluate this group because an observation of less than three years is too short to exclude the possibility of future dissemination of the disease process

Apart from these three groups the authors found, in the literature, forty-five more cases which could not be adequately classified Many of these cases had only a short follow up; the others had not been examined completely. Most of them had been diagnosed erroneously

as solitary plasmocytomas, although from the onset there had been signs of disseminated myelomatosis. None of these cases had either appreciable increase of the globulins of the serum or rouleaux formation However, in three cases of the first two groups, Bence Jones proteinuria could be detected.

Dalgaard and Dalgaard[43] reported recently on three cases of solitary plasmocytoma of the spine with terminal dissemination. Their first patient showed signs of generalization nine years after the onset of pain in the back due to a plasmocytoma of the second lumbar vertebra. The second case died within five years of generalization of the myeloma. The third case had a large plasmocytoma of the third lumbar vertebra, but five months later many osteolytic areas were observed in the skull and the bone marrow puncture was positive for myeloma cells These three cases emphasize the point made by Lichtenstein and Jaffe[105] that, as the number of survivors falls off from year to year, very few of what originally seemed to be true cases of solitary myeloma remain at the end of a ten year period of observation. Nevertheless, cases with a survival period of seven and a half, eight, and twelve years have been reported. In this connection it is interesting to note that in a report on sixty-six cases of myeloma from Montefiore Hospital, where patients are followed for extremely long periods of time, no example of "solitary myeloma" remaining solitary was found The rarity of the condition is emphasized by Bayrd and Heck[19] who found that in each of their cases where the diagnosis of solitary myeloma was considered, sternal marrow aspiration revealed evidence of generalized myelomatosis Notwithstanding this experience, they feel that rare cases of solitary myeloma actually do occur.

An interesting approach to the clarification of this problem has been made by Lane[101] in his study of a patient with a solitary plasmocytoma of the mandible. This patient had no Bence Jones proteinuria, the serum albumin was 5.3 Gm. per cent, and the serum globulin 1.7 Gm. per cent. Careful electrophoretic analysis of the serum before operation, however, revealed the presence of a small but abnormally sharp gamma peak Following the removal of the tumor, electrophoresis was repeated at monthly intervals. Within two months the apex of the serum globulin curve became less sharp, and five months after the operation the curve was entirely normal. In addition, electrophoretic analysis of the tumor showed that the main part of the protein consisted of gamma globulin and that the

gamma globulin portion of the electrophoretic curve obtained from the tumor proteins could be superimposed exactly upon the corresponding curve shown by the serum of the patient before operation

The results reported in this case could well be of fundamental importance, if the changes in the electrophoretic pattern before and after operation are accepted as significant Unfortunately the abnormal gamma peak in the preoperative curve is small Before drawing far reaching conclusions, Lane's observation should be confirmed in other cases of solitary myeloma with more marked changes in the electrophoretic pattern Such observations would indicate that the abnormal globulins are actually manufactured within the plasmocytoma itself and would support the original theory of Magnus-Levy It is within the realm of possibility that not only abnormal globulins, but also Bence Jones protein is produced by the tumor itself This would explain the presence of Bence Jones proteinuria in patients with a large solitary myeloma, confirmed by autopsy The alternate explanation would be that the body reacts to the presence of the plasmocytoma by producing abnormal globulins, but this is unlikely since the abnormal globulins could be extracted from the tumor tissue itself

It should be added that an observation such as Lane's does not preclude the possibility that, in such cases, a generalization of the myeloma process may occur at a later date It only suggests that the main source of abnormal serum globulins was present in the plasmocytoma removed It is certainly possible that in other parts of the skeleton small microscopic nests of myeloma cells were present, too minute to produce detectable amounts of abnormal proteins. Such minimal cell nests may later give rise to macroscopic lesions Be this as it may, one of the characteristic qualities of myeloma, that is, the production of abnormal proteins, would appear to be present, though only in rare instances, in the solitary myeloma as well as in generalized myelomatosis

In this series no case could be considered unequivocally as a solitary myeloma Three cases with single myelomatous lesions with negative sternal marrow aspirations later developed roentgen evidence of other bone involvement Two patients with cord signs had myelomatous tumors partially removed at laminectomy with amelioration of symptoms Both had repeatedly negative marrow aspirations, though one had disseminated lytic lesions on x-ray and, in the fifth

year of her disease, died with diffuse involvement. The other patient (p. 33), now in the second year of the disease, still shows no sign of dissemination of the disease process. The undoubted occurrence of numerous cases which at first appear to have a single focus of myeloma tissue, casts some doubt on the multicentric theory of origin of all cases of multiple myeloma Surgical resection of a localized tumor before the occurrence of "metastases", as was done in the case reported by Stewart and Taylor[189] and that reported by Lane,[101] should be recommended in the hope that such a lesion is truly solitary.

8. MULTIPLE PLASMOCYTOMAS

Until the present time two clinical entities have been recognized. One, the most common form, is the generalized myelomatosis in which bone marrow puncture reveals generalized plasma cell infiltration throughout the entire skeleton. The other entity is the rare solitary myeloma, which is an isolated plasmocytoma with no tendency to generalization. Between these two extremes, an intermediary form seems to exist, which is characterized by the presence of several isolated plasmocytomas. This clinical entity differs from generalized myelomatosis in that the bone marrow distant from the lesions is free of any evidence of plasma cell proliferation. Strictly speaking, the name multiple myeloma should perhaps be reserved for the rare cases which fall in this category, whereas the disease which is commonly designated as multiple myeloma could better be named generalized myelomatosis. The literature contains several examples of extramedullary plasmocytomas, giving rise to multiple separate plasmocytomas in the skeleton persisting for many years until finally generalized myelomatosis developed.[82] Observations of patients with multiple plasmocytomas, but without generalized myelomatous infiltrations of the bone marrow, are few and far between. The following observation is a good example of this rare clinical entity.

In 1946, a 39 year old man developed a small and circumscribed swelling of the nasal process of the right maxillary bone. A biopsy proved this to be a plasmocytoma of the nasal bone. Urine, total blood count, sedimentation rate, serum albumin, and globulin were completely normal. Local radiotherapy was given. In 1949, he developed pain in the left clavicle and x-ray examination of this bone revealed the presence of an osteolytic lesion. At this time, total blood count and determinations of serum albumin (4.7 Gm. per cent) and globulin (3.3 Gm. per cent) were again within normal limits. The sedimenta-

tion rate of the red cells was 5 mm per hour. There was no Bence Jones protein in the urine, and sternal marrow aspiration failed to show a picture of myelomatosis The tumor of the clavicle was resected and was proven by pathologic examination to be a plasmocytoma. Microscopic study of both ends of the bone specimen were found to be completely normal After the operation radiotherapy was directed to the operated area.

In June 1949 a tender spot developed at the left margin of the sternum and in July 1949 the patient noticed, after sneezing, a sharp stabbing pain in both sides of the lower back Roentgen examination revealed, both in the right and in the left tenth rib, the presence of an osteolytic lesion, with a pathologic fracture running across the decalcified area In addition, a small irregularly rounded lesion, one-fourth of an inch in diameter, was seen in the right parietal bone Finally an area of destruction was formed at the left margin of the body of the sternum

The patient suffered a considerable amount of pain—especially in the back, but also in other areas. In July 1949 he was started on urethane. By October 1949 the severe aches and pains had disappeared but transient minor aches, especially in the left shoulder, persisted On November 8th, 1949 a total of 240 Gm. of urethane had been taken. For the next three years the patient was given 1 Gm of urethane daily every other month and 25 mg of testosterone twice weekly by intramuscular injection during the alternate months Under this treatment he felt quite well, especially during the months when he took testosterone. During the urethane months, he occasionally complained of aching and muscle twitching.

marrow punctures revealed a cellular bone marrow with a normal amount of megakaryocytes. Again no myeloma cells were present. Radiologic survey of the skeleton revealed healed fractures of both the right and left tenth ribs There was good callus formation and the osteolytic areas had completely disappeared The rounded osteolytic area in the parietal bone and also the lesion at the left side of the body of the sternum had completely filled in Despite this improvement and encouraging progress, however, a new plasmo- [illegible] phalanx of the right index finger an

the lesion was a recent one

no Bence Jones

ge, possibly the

plus glycosuria

with a fasting blood sugar of 165 mg per cent on one occasion. Glucose tolerance test was normal The cephalin flocculation test was 2 plus after 48 hours The bromsulphalein test showed a retention of 2 5 per cent after 30 minutes The alkaline phosphatase was 7.5 Bodansky Units (in October 1950, 6 King-Armstrong units)

In November 1952 he developed a very severe herpes zoster over the right [illegible]

[illegible]

were completely normal, Bence Jones protein absent, and the serum alkaline phosphatase nearly normal (5 Bodansky units) Sternal marrow was again found to be normal

In this patient, therefore, at least seven plasmocytomas have been discovered during the seven year course of his disease (table 12) Nevertheless, his general condition has remained excellent; repeatedly negative sternal bone marrow punctures indicated that there was no generalized myelomatous infiltration of the bone marrow The blood proteins were normal and Bence Jones protein absent. This patient could well be considered an example of multiple plasmocytomas without generalized myelomatosis The patient reacted favorably to urethane administration However, after three and one-half years of intermittent urethane treatment hepatosplenomegaly had developed and there was suggestive evidence of cirrhosis of the liver

The second case which may belong to this group apparently had plasmocytomas of several vertebrae The rest of the skeleton was initially free of roentgenologic lesions, although, in contrast to the foregoing case, Bence Jones proteinuria and hyperglobulinemia were present. Bone marrow puncture was repeatedly negative until three years after the onset of the disease.

[illegible]

of the first lumbar vertebrae The urine repeatedly contained Bence Jones protein The serum albumin was 2 8 Gm per cent, serum globulin 6 9 Gm per

TABLE 12.—*A B —A Case of Multiple Plasmocytomas, Treated for over Three Years with Urethane*

Date	Hgb.	Alb	Glob.	ESR	Remarks
Jan 1946		5 0	2 0		Plasmocytoma of Nasal Bone
Jan 1949	15 2	4 7	2 3	5	Plasmocytoma of Clavicle resected. Sternal marrow aspiration normal Bence Jones protein negative
June 1949		4 3	2 0		
Aug 1949					Plasmocytomas R and L tenth rib, skull, and sternum Sternal marrow aspiration normal Urethane started
Dec 1949	19	4 7	3 0		240 Gm of Urethane taken
March 1950	18 5	4 8	3 4	2	
Oct 1950	17.4	4 1	2 4	20	Lesions in both tenth ribs and sternum filled in. Fresh plasmocytoma in R index finger Sternal marrow aspiration normal Bence Jones protein negative
Dec 1950					Started taking on alternate months—2 Gm. of Urethane daily or 25 mg Testosterone Propionate intramuscularly twice weekly
March 1952	17 8	4 5	3 2	12	General condition excellent Roentgenologic skeletal survey as in October 1950. Bence Jones protein negative
Feb 1953	14 7	5 1	1 9	12	Urethane discontinued because of signs of liver damage and hepatosplenomegaly General condition still good Marrow normal

cent A sternal marrow puncture was done, but myeloma cells could not be found Nevertheless, a diagnosis of multiple myeloma was made and the patient was started on 4 Gm of urethane daily. He responded well and did not develop gastrointestinal disturbances Shortly after the institution of the urethane treatment the pains in the back disappeared and after one month, in the middle of June, the patient was able to get up for short intervals during the day

Examination in July 1950 revealed that the patient had almost no residual pain The hemoglobin was 11 9 Gm , the red cells 3,800,000, and the leukocytes 3600, with a normal differential count Bence Jones protein was present in moderate amounts Serum albumin was 2 2 and 2 3 Gm per cent, serum globulin 4.8 and 5 1 Gm per cent. The sedimentation rate of the red blood cells was 126 mm per hour Sternal marrow examination again failed to demonstrate the presence of myeloma cells

On x-ray examination considerable decalcification of the entire spine and an hour glass appearance of many of the vertebral bodies were found, most marked in the lumbar region The remaining bones showed no gross abnormalities. Although the patient's general condition had improved considerably, the local condition of the spine, if anything, had deteriorated. It was, therefore,

decided to stop the urethane, and ACTH therapy, 40 mg daily was begun. On this treatment the patient did exceedingly well for two and one-half years In November 1950, the serum albumin was 3 9 Gm per cent, the serum globulin 5 7 Gm per cent.

In July 1951 a bone marrow puncture showed normal findings except for a slight increase in erythroid elements. Only a rare plasma cell was seen The serum albumin was 3.2 Gm. per cent, the serum globulin 4 6 Gm. per cent, and a moderate amount of Bence Jones protein was still found in the urine In August 1951 the condition was so satisfactory that it was decided to decrease the ACTH administration to three weekly injections of 20 mg In November 1951 the patient accepted a new business position with many responsibilities which he was able to discharge without difficulty In July 1952, roentgen examination showed a considerable increase in the concavity of the superior and inferior aspects of the lower dorsal and lumbar vertebral bodies with widening of the intravertebral spaces. There was moderate decalcification of the vertebral bodies, but well defined destructive lesions were nowhere to be seen

In November 1952, the back pain returned and the patient began to go downhill despite an increased dose of ACTH and the addition of 3 Gm of urethane daily. In the beginning of January 1953 the spasms of terrific pain were as severe as at the onset of this disease three years previously A non-tender, soft tissue swelling was found next to the thoracic spine extending from T 7 to T 12. Laboratory examination showed the presence of a sedimentation rate of 116 mm per hour Serum albumin was 2 2 Gm. per cent, serum globulin 7 Gm. per cent. The blood urea nitrogen was 40 mg per cent. The urine contained 3 plus albumin but this time Bence Jones protein was not found Serum calcium and phosphorus levels were normal. The alkaline phosphatase content was 6 King-Armstrong units.

Urethane was continued and in February 1953 the patient again had a remission of his pain A new sternal marrow puncture at this time finally showed the presence of multiple myeloma.

TABLE 13.—*R.D.—A Case of Multiple Plasmocytomas, Treated for Two Months with Urethane, and Then for Two and One Half Years with ACTH*

Date	Alb	Glob	B.J.	
May, 1950	2 8	6 9	+	
July, 1950	2 2	5 1		Urethane
August, 1950	3 0	5 5	+	ACTH
November, 1950	3 9	5 7	+	ACTH
July, 1951	3 2	4 6	+	ACTH
February, 1952	3 8	4 6	+	ACTH
January, 1953	2 2	7.0	−	Urethane

Sternal marrow punctures in May and July 1950 and in February 1952 were all negative.

Sternal marrow puncture in February 1953 showed the presence of multiple myeloma.

The typical x-ray picture in combination with the hyperglobulinemia and the presence of Bence Jones protein, made the diagnosis

TABLE 12 —*A.B —A Case of Multiple Plasmocytomas, Treated for over Three Years with Urethane*

Date	Hgb.	Alb	Glob	ESR	Remarks
Jan 1946		5 0	2 0		Plasmocytoma of Nasal Bone
Jan 1949	15 2	4 7	2 3	5	Plasmocytoma of Clavicle resected. Sternal marrow aspiration normal Bence Jones protein negative
June 1949		4 3	2 0		
Aug 1949					Plasmocytomas R and L tenth rib, skull, and sternum Sternal marrow aspiration normal Urethane started
Dec 1949	19	4 7	3 0		240 Gm of Urethane taken
March 1950	18 5	4 8	3 4	2	
Oct 1950	17 4	4 1	2 4	20	Lesions in both tenth ribs and sternum filled in Fresh plasmocytoma in R. index finger Sternal marrow aspiration normal. Bence Jones protein negative
Dec 1950					Started taking on alternate months—2 Gm. of Urethane daily or 25 mg Testosterone Propionate intramuscularly twice weekly
March 1952	17 8	4 5	3 2	12	General condition excellent Roentgenologic skeletal survey as in October 1950 Bence Jones protein negative
Feb 1953	14 7	5 1	1 9	12	Urethane discontinued because of signs of liver damage and hepatosplenomegaly General condition still good Marrow normal

cent A sternal marrow puncture was done, but myeloma cells could not be found Nevertheless, a diagnosis of multiple myeloma was made and the patient was started on 4 Gm of urethane daily He responded well and did not develop gastrointestinal disturbances Shortly after the institution of the urethane treatment the pains in the back disappeared and after one month, in the [illegible]
[illegible]
[illegible]
cytes 3600, with a normal differential count Bence Jones protein was present in moderate amounts Serum albumin was 2 2 and 2 3 Gm. per cent, serum globulin 4.8 and 5 1 Gm per cent. The sedimentation rate of the red blood cells was 126 mm per hour Sternal marrow examination again failed to demonstrate the presence of myeloma cells

On x-ray examination considerable decalcification of the entire spine and an hour glass appearance of many of the vertebral bodies were found, most marked in the lumbar region. The remaining bones showed no gross abnormalities Although the patient's general condition had improved considerably, the local condition of the spine, if anything, had deteriorated It was, therefore,

decided to stop the urethane, and ACTH therapy, 40 mg. daily was begun On this treatment the patient did exceedingly well for two and one-half years In November 1950, the serum albumin was 3.9 Gm per cent, the serum globulin 5.7 Gm per cent

In July 1951 a bone marrow puncture showed normal findings except for a slight increase in erythroid elements Only a rare plasma cell was seen. The serum albumin was 3 2 Gm per cent, the serum globulin 4 6 Gm per cent, and a moderate amount of Bence Jones protein was still found in the urine. In August 1951 the condition was so satisfactory that it was decided to decrease the ACTH administration to three weekly injections of 20 mg. In November 1951 the patient accepted a new business position with many responsibilities which he was able to discharge without difficulty In July 1952, roentgen examination showed a considerable increase in the concavity of the superior and inferior aspects of the lower dorsal and lumbar vertebral bodies with widening of the intravertebral spaces There was moderate decalcification of the vertebral bodies, but well defined destructive lesions were nowhere to be seen

In November 1952, the back pain returned and the patient began to go downhill despite an increased dose of ACTH and the addition of 3 Gm of urethane daily In the beginning of January 1953 the spasms of terrific pain were as severe as at the onset of this disease three years previously A nontender, soft tissue swelling was found next to the thoracic spine extending from T 7 to T 12 Laboratory examination showed the presence of a sedimentation rate of 116 mm per hour Serum albumin was 2 2 Gm per cent, serum globulin 7 Gm per cent The blood urea nitrogen was 40 mg per cent The urine contained 3 plus albumin but this time Bence Jones protein was not found Serum [illegible]

[illegible]

the presence of multiple myeloma

TABLE 13 —*R D —A Case of Multiple Plasmocytomas, Treated for Two Months with Urethane, and Then for Two and One Half Years with ACTH*

Date	Alb	Glob	B J	
May, 1950	2 8	6 9	+	
July, 1950	2 2	5 1		Urethane
August, 1950	3 0	5 5	+	ACTH
November, 1950	3 9	5 7	+	ACTH
July, 1951	3 2	4 6	+	ACTH
February, 1952	3 8	4 6	+	ACTH
January, 1953	2 2	7 0	—	Urethane

Sternal marrow punctures in May and July 1950 and in February 1952 were all negative

Sternal marrow puncture in February 1953 showed the presence of multiple myeloma

The typical x-ray picture in combination with the hyperglobulinemia and the presence of Bence Jones protein, made the diagnosis

TABLE 12 — A B — *A Case of Multiple Plasmocytomas, Treated for over Three Years with Urethane*

Date	Hgb.	Alb	Glob	ESR	Remarks
Jan 1946		5 0	2 0		Plasmocytoma of Nasal Bone
Jan 1949	15 2	4 7	2 3	5	Plasmocytoma of Clavicle resected Sternal marrow aspiration normal Bence Jones protein negative
June 1949		4 3	2 0		
Aug 1949					Plasmocytomas R and L tenth rib, skull, and sternum Sternal marrow aspiration normal Urethane started
Dec 1949	19	4 7	3 0		240 Gm of Urethane taken
March 1950	18 5	4 8	3 4	2	
Oct 1950	17 4	4 1	2 4	20	Lesions in both tenth ribs and sternum filled in Fresh plasmocytoma in R. index finger Sternal marrow aspiration normal Bence Jones protein negative
Dec 1950					Started taking on alternate months—2 Gm. of Urethane daily or 25 mg Testosterone Propionate intramuscularly twice weekly
March 1952	17 8	4 5	3 2	12	General condition excellent Roentgenologic skeletal survey as in October 1950 Bence Jones protein negative
Feb. 1953	14 7	5 1	1 9	12	Urethane discontinued because of signs of liver damage and hepatosplenomegaly General condition still good Marrow normal

cent A sternal marrow puncture was done, but myeloma cells could not be found Nevertheless, a diagnosis of multiple myeloma was made and the patient was started on 4 Gm of urethane daily He responded well and did not develop gastrointestinal disturbances. Shortly after the institution of the urethane treatment the pains in the back disappeared and after one month, in the middle of June, the patient was able to get up for short intervals during the day.

Examination in July 1950 revealed that the patient had almost no residual pain The hemoglobin was 11 9 Gm , the red cells 3,800,000, and the leukocytes 3600, with a normal differential count Bence Jones protein was present in moderate amounts Serum albumin was 2 2 and 2.3 Gm per cent, serum globulin 4 8 and 5.1 Gm per cent The sedimentation rate of the red blood cells was 126 mm per hour Sternal marrow examination again failed to demonstrate the presence of myeloma cells

On x-ray examination considerable decalcification of the entire spine and an hour glass appearance of many of the vertebral bodies were found, most marked in the lumbar region The remaining bones showed no gross abnormalities. Although the patient's general condition had improved considerably, the local condition of the spine, if anything, had deteriorated. It was, therefore,

decided to stop the urethane, and ACTH therapy, 40 mg. daily was begun On this treatment the patient did exceedingly well for two and one-half years In November 1950, the serum albumin was 3 9 Gm per cent, the serum globulin 5.7 Gm per cent

August 1951 the condition was so satisfactory that it was decided to decrease

bral bodies, but well defined destructive lesions were nowhere to be seen

In November 1952, the back pain returned and the patient began to go downhill despite an increased dose of ACTH and the addition of 3 Gm of urethane daily In the beginning of January 1953 the spasms of terrific pain were as severe as at the onset of this disease three years previously A non-tender, soft tissue swelling was found next to the thoracic spine extending from T 7 to T 12 Laboratory examination showed the presence of a sedimentation rate of 116 mm per hour Serum albumin was 2 2 Gm per cent, serum globulin 7 Gm per cent The blood urea nitrogen was 40 mg per cent The urine contained 3 plus albumin but this time Bence Jones protein was not found Serum *calcium and phosphorus levels were normal The alkaline phosphatase content* was 6 King-Armstrong units

Urethane was continued and in February 1953 the patient again had a remission of his pain A new sternal marrow puncture at this time finally showed the presence of multiple myeloma

TABLE 13 —*R D —A Case of Multiple Plasmocytomas, Treated for Two Months with Urethane, and Then for Two and One Half Years with ACTH*

Date	Alb	Glob	B J	
May, 1950	2 8	6 9	+	
July, 1950	2 2	5 1		Urethane
August, 1950	3 0	5 5	+	ACTH
November, 1950	3 9	5 7	+	ACTH
July, 1951	3 2	4 6	+	ACTH
February, 1952	3 8	4 6	+	ACTH
January, 1953	2 2	7 0	−	Urethane

Sternal marrow punctures in May and July 1950 and in February 1952 were all negative

Sternal marrow puncture in February 1953 showed the presence of multiple myeloma

The typical x-ray picture in combination with the hyperglobulinemia and the presence of Bence Jones protein, made the diagnosis

TABLE 12 —*A B.—A Case of Multiple Plasmocytomas, Treated for over Three Years with Urethane*

Date	Hgb	Alb	Glob	ESR	Remarks
Jan 1946		5 0	2 0		Plasmocytoma of Nasal Bone
Jan 1949	15 2	4 7	2 3	5	Plasmocytoma of Clavicle resected. Sternal marrow aspiration normal Bence Jones protein negative
June 1949		4 3	2 0		
Aug 1949					Plasmocytomas R and L tenth rib, skull, and sternum. Sternal marrow aspiration normal Urethane started
Dec. 1949	19	4 7	3 0		240 Gm of Urethane taken
March 1950	18 5	4 8	3 4	2	
Oct 1950	17 4	4 1	2 4	20	Lesions in both tenth ribs and sternum filled in Fresh plasmocytoma in R. index finger Sternal marrow aspiration normal Bence Jones protein negative
Dec 1950					Started taking on alternate months—2 Gm. of Urethane daily or 25 mg. Testosterone Propionate intramuscularly twice weekly
March 1952	17 8	4 5	3 2	12	General condition excellent Roentgenologic skeletal survey as in October 1950. Bence Jones protein negative
Feb. 1953	14 7	5 1	1 9	12	Urethane discontinued because of signs of liver damage and hepatosplenomegaly General condition still good Marrow normal

cent A sternal marrow puncture was done, but myeloma cells could not be found Nevertheless, a diagnosis of multiple myeloma was made and the patient was started on 4 Gm of urethane daily He responded well and did not

pain The hemoglobin was 11 9 Gm , the red cells 3,800,000, and the leukocytes 3600, with a normal differential count Bence Jones protein was present

an hour glass appearance of many of the vertebral bodies were found, most marked in the lumbar region The remaining bones showed no gross abnormalities Although the patient's general condition had improved considerably, the local condition of the spine, if anything, had deteriorated It was, therefore,

9. EXTRAMEDULLARY PLASMOCYTOMAS

Hellwig[79] collected many cases of extramedullary plasma cell tumors, which are histologically identical to the plasmocytomas of the bone marrow They have a peculiar predilection for the upper air passages but occasionally occur in the stomach, intestine, pancreas, pleura, thyroid, urogenital tract, and skin. In the majority of these cases, the plasmocytomas remained localized, nevertheless, in a number of cases the tumor definitely did invade adjacent tissues and was neoplastic in nature Metastases to lymph nodes and to bone were not infrequent Ultimately the complete picture of multiple myeloma may emerge from this tumor Bence Jones proteinuria has never been reported in cases of extramedullary plasmocytoma without skeletal involvement.

Several of these cases have remarkably long follow ups, the longest in Hellwig's series being eighteen years A patient of Jackson[82] who was operated on in 1919 for a plasmocytoma of the left tonsil developed a similar tumor of the right tonsil two years later and in 1926 all the signs of a classical multiple myeloma were present A case of an extramedullary plasmocytoma with a remarkably benign course was observed by Jaeger [87] His patient had a plasmocytoma of the epipharynx In the course of eight years, four local recurrences were successfully treated with radiotherapy. In neither the original tumor nor in any of the recurrences were the regional lymph nodes involved During the next nine years, plasmocytomas appeared in the skull, sternum, ribs, both clavicles, humeri, right scapula, right tibia, and thyroid gland Bence Jones protein could never be found in the urine The serum proteins remained normal. The patient's condition was excellent twenty-five years after the first plasmocytoma was discovered. Jaeger's reluctance to classify this case as one of multiple

of multiple plasmocytomas almost a certainty, even during the three years when no myeloma cells could be found in the bone marrow. In view of the three negative sternal marrow punctures, it is likely that generalized infiltration of the bone marrow was not present and that this patient suffered during these years from multiple plasmocytomas of the spine Then, after three years, generalization of the myelomatous process occurred with an acceleration of his downhill course.

tiva are perhaps more properly called plasma cell granulomas Some leukocytes, lymphocytes, and fibroblasts, but predominantly plasma cells, are found in these masses. Hellwig reports on fifty such cases and Chojnakci[33a] found about one hundred cases Most authors are of the opinion that these tumors are inflammatory in nature and that their neoplastic characteristics—if they have any at all—are indistinct since they are neither destructive nor invasive

myeloma, despite the typical anatomic structure of the bone marrow, can easily be understood

One case of plasmocytoma of the nasal cavity, which was followed up for three years without generalization, has been studied in this hospital by Rosenwasser.[152]

This patient was admitted in August 1929, complaining of left sided nasal obstruction which had troubled him throughout the previous year. At the same time a foul smelling nasal discharge had developed A soft whitish mass was seen at the left side above the inferior meatus This friable, easily bleeding mass seemed to rise from the lateral part of the nose. X-ray of the sinuses revealed a cloudiness of the left antrum, ethmoid, and sphenoid and a slight cloudiness of the right ethmoid On two separate occasions the tumor was biopsied and reported to be a plasmocytoma Three radium seeds with a platinum filter were placed in the tumor mass and left in place for ten days This was followed by a course of deep x-ray therapy The tumor mass diminished markedly in size so that ultimately the patient had an adequate airway and relief of almost all symptoms Two months later a histologic examination of a biopsy specimen taken from the site of the original tumor was negative. The plasmocytoma had evidently disappeared following radiation

In September 1930, the patient had numerous small nasal hemorrhages from the left side of the nose Following his discharge, the patient had received intermittent radiotherapy There was now definite local evidence of involvement of the left antrum and ethmoids A Caldwell-Luc operation was performed and radium was inserted directly into the antrum and floor of the nose. The excised tumor tissue was again reported to be a plasmocytoma Postoperative radiotherapy was given with relief of epistaxis and nasal obstruction.

In 1932, almost three years after the original treatment was begun, the patient complained of weight loss, anorexia, and abdominal discomfort X-ray examination revealed a huge mass in the fundus of the stomach, which had invaded the lower end of the esophagus He died of cachexia with terminal bilateral bronchopneumonia

The findings at autopsy consisted of carcinoma of the stomach with metastases to the liver, pancreas, pleura, and regional lymph nodes, bilateral bronchopneumonia, pulmonary emphysema, hypertrophy and dilatation of the right heart, mild bronchiectasis, healed apical tuberculosis, and terminal endocarditis of the aortic valve There was no evidence of recurrence of the plasmocytoma, despite a careful search

This patient with a plasmocytoma of the nasal cavity was carefully followed for over three years As usual this extramedullary plasmocytoma, though it did not metastasize or involve the regional lymph nodes, could not be eradicated surgically. Optimal results were obtained by the combination of surgery and radiotherapy. When this patient died of carcinoma of the stomach, no recurrence of the plasmocytoma could be detected.

In contrast to plasmocytomas, plasma cell tumors of the conjunc-

tiva are perhaps more properly called plasma cell granulomas Some leukocytes, lymphocytes, and fibroblasts, but predominantly plasma cells, are found in these masses. Hellwig reports on fifty such cases and Chojnakci[33] found about one hundred cases. Most authors are of the opinion that these tumors are inflammatory in nature and that their neoplastic characteristics—if they have any at all—are indistinct since they are neither destructive nor invasive.

10. PATHOLOGY

The plasmocytomas found in multiple myeloma have a predilection for those bones with abundant cancellous spongiosa and red marrow, such as the pelvis, spine, sternum, skull, and long bones Pathologic examination of the bones, particularly of the sternum, vertebrae, and ribs often reveals marked thinning of the cortex Rather frequently the cortex is completely eroded and the bulging myelomatous tumor tissue may actually infiltrate the surrounding musculature Destruction and disorganization of the bone trabeculae allow the bone to be cut easily with the knife The bone may be brittle in some cases, while in others it may be bent without fracture The medullary cavity of the bone is, in many areas, replaced by round or oval, clear cut masses of grey or purple gelatinous tumor tissue which may be scooped out readily (figs 11a, 38). Often the plasmocytomas are hemorrhagic in character Dalrymple,[44] in the original pathologic description, spoke of "large cancellous cavities filled by a red gelatiniform substance, threaded here and there by fine bony fibres" Occasionally a focus of myeloma tissue may grow rapidly and produce marked expansion of a bone and a large palpable soft tissue tumor. Such tumor masses are extremely vascular and occasionally produce an arterial bruit. Tumors of this type have been described as being pulsatile. The largest of these plasmocytomas are found in the pelvis, arising from the iliac wings, but large tumors may also be present in the long bones and in the vertebrae. The plasmocytomas of the spine have a tendency to cause compression of the spinal cord. Expanding tumors of the calvarium, although rare, may be found if a myeloma in the diploic space perforates the tables of the skull to erupt either under the scalp or subdurally. Myelomatous tumors of the scalp are usually soft. Multiple firm and hard tumors of

the scalp are usually due to reticulum cell sarcomas or lymphomas, occasionally due to chloroleukemia or true neoplasms Microscopically, one sees a monotonous picture of closely packed young plasma cells with scanty stroma and eccentric nuclei. Mitotic figures do occur, but are, in most cases, relatively rare



FIG 37.—(*a*) Pathologic specimen of femur diffusely infiltrated by myeloma Note the destruction of the trabecular pattern and erosion of the cortex (*b*) Washed specimen

Extraskeletal myelomatous involvement is not as uncommon as was originally thought and has been reported frequently in the literature [36,37,66,82,111] Nodular infiltrations of liver, spleen, and lymph nodes have been frequently described, as have myelomatous infiltration of the kidney, pancreas, lungs, adrenal, thyroid, tonsil, intestine, gonads, muscle, and brain Churg and Gordon[36] found twenty-two

of thirty consecutive cases of multiple myeloma, autopsied at the Mount Sinai Hospital, to have myeloma cell aggregates in the liver, spleen, and lymph nodes. Ten of these cases demonstrated gross involvement In addition, in nine of the thirty cases, organs other than those of the extraosseous hematopoietic system were involved. In only eight of the thirty cases studied by Churg and Gordon could they find no visceral involvement at all. These myelomatous foci may take the form of discrete plasma cell nodules or they may occur as a diffuse

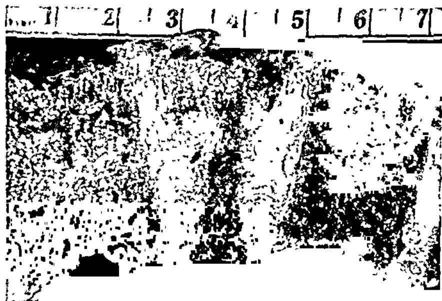


FIG 38 —Pathologic specimen demonstrating collapse of vertebral body infiltrated by multiple myeloma Note the gelatinous appearance of the marrow.

infiltration of the organs similar to the situation in leukemia or reticulum cell sarcoma Gross myelomatous involvement of the viscera was found in fifteen of the forty-one autopsied cases in this series The most common sites of extraskeletal myelomatous involvement were the lymph nodes, spleen, and liver, these organs were infiltrated almost twice as frequently as all the other organs combined (fig. 19).

The cutaneous manifestations of multiple myeloma often take a curious pattern Umbilicated and ulcerated nodules infiltrating the skin and producing a picture resembling mycosis fungoides have been described by Duvoir et al.[57] and by Kin.[92] Piney and Riach[142] have reported an unusual case of skin involvement, in which a diffuse

nodular infiltration resembling neurofibromatosis covered the skin of trunk and limbs while the scalp, forehead, temples, and neck were covered in helmet-like fashion by infiltrating myelomatous tumors The patient also suffered from plasma cell leukemia One patient in our series developed numerous subcutaneous nodules several weeks before her death Autopsy showed extensive plasma cell infiltration of the viscera (p 46).

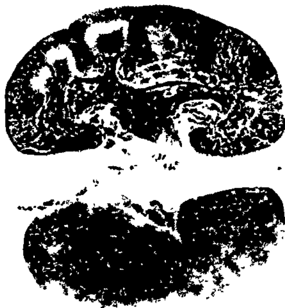


FIG 39—Gross specimen of myeloma kidney Despite the almost normal gross appearance of the kidney, the patient died with severe uremia and a blood urea nitrogen of 130 mg per cent

Grossly, the myeloma kidney is pale and smooth. It may be contracted but more frequently it is normal in size or even somewhat enlarged. From gross examination, one could hardly predict that such a kidney could be responsible for severe uremia (fig. 39). Microscopic examination reveals edema and an interstitial infiltration with mononuclear cells However, the outstanding histologic feature is the presence of dense, acidophilic casts plugging the tubules and sur-

of thirty consecutive cases of multiple myeloma, autopsied at the Mount Sinai Hospital, to have myeloma cell aggregates in the liver, spleen, and lymph nodes. Ten of these cases demonstrated gross involvement In addition, in nine of the thirty cases, organs other than those of the extraosseous hematopoietic system were involved In only eight of the thirty cases studied by Churg and Gordon could they find no visceral involvement at all These myelomatous foci may take the form of discrete plasma cell nodules or they may occur as a diffuse

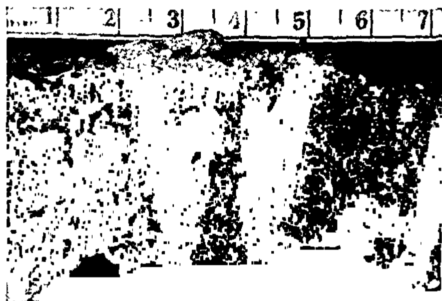


FIG. 38 —Pathologic specimen demonstrating collapse of vertebral body infiltrated by multiple myeloma Note the gelatinous appearance of the marrow.

infiltration of the organs similar to the situation in leukemia or reticulum cell sarcoma. Gross myelomatous involvement of the viscera was found in fifteen of the forty-one autopsied cases in this series. The most common sites of extraskeletal myelomatous involvement were the lymph nodes, spleen, and liver; these organs were infiltrated almost twice as frequently as all the other organs combined (fig. 19).

The cutaneous manifestations of multiple myeloma often take a curious pattern Umbilicated and ulcerated nodules infiltrating the skin and producing a picture resembling mycosis fungoides have been described by Duvoir et al.[57] and by Kin.[92] Piney and Riach[142] have reported an unusual case of skin involvement, in which a diffuse

nodular infiltration resembling neurofibromatosis covered the skin of trunk and limbs while the scalp, forehead, temples, and neck were covered in helmet-like fashion by infiltrating myelomatous tumors The patient also suffered from plasma cell leukemia. One patient in our series developed numerous subcutaneous nodules several weeks before her death. Autopsy showed extensive plasma cell infiltration of the viscera (p. 46).



FIG 39 —Gross specimen of myeloma kidney. Despite the almost normal gross appearance of the kidney, the patient died with severe uremia and a blood urea nitrogen of 130 mg per cent

Grossly, the myeloma kidney is pale and smooth. It may be contracted but more frequently it is normal in size or even somewhat enlarged. From gross examination, one could hardly predict that such a kidney could be responsible for severe uremia (fig 39) Microscopic examination reveals edema and an interstitial infiltration with mononuclear cells However, the outstanding histologic feature is the presence of dense, acidophilic casts plugging the tubules and sur-

rounded by foreign body giant cells (figs. 14, 15). Often these casts appear to be brittle as if they had been fractured by the microtome. They frequently show lamellated and calcified centers (fig. 40). These casts do not take the stains for amyloid. Allen[5] believes that the surrounding multinucleated cells actually represent a syncytium of tubular epithelial cells rather than true foreign body giant cells. The proximal tubules may show slight dilatation, but more often there is conspicuous atrophy The glomeruli may be remarkably normal and the vessels show no change, unless amyloid is present. Sikl[172] and

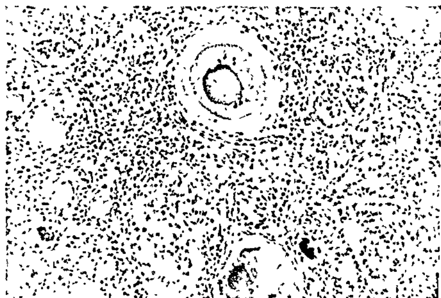


Fig 40.—Myeloma kidney with large lamellated cast

Apitz[8] have published beautiful microphotographs of needle-like crystals in association with these tubular casts and within the tubular epithelial cells. Crystalline deposits in myeloma tissue were first described by Glaus,[67] and Lohlein[110] was the first to describe crystalline tubular casts in multiple myeloma

When amyloidosis is associated with multiple myeloma, as it is in about 10 per cent of the cases, the distribution is that of primary systemic amyloidosis and is often called paramyloidosis. This paramyloid is deposited in the mesenchymal tissues as opposed to the massive involvement of liver, spleen, kidney, adrenal, and blood vessel walls seen in the amyloidosis secondary to chronic suppuration or tubercu-

losis Primary amyloid frequently stains poorly with the metachromatic dyes, Congo red, methyl violet, and iodine green. Blood vessels are conspicuously involved in the paramyloidosis of myeloma (fig. 32). The gastrointestinal tract from oropharynx to rectum may be diffusely infiltrated but here, also, the involvement may be primarily localized in the arteries Nodular amyloidosis of the larynx, joint capsules, (fig 35), and skin occurs One female patient in this series demonstrated the unusual complication of almost complete baldness due to amyloid deposition in the scalp. Another patient had widespread subcutaneous amyloid tumors over the lower chest and upper abdomen. Skeletal muscle and the striated muscle of the myocardium are frequently involved, as is the auricular endocardium (fig 32a) The infiltration of the heart muscle is often massive enough to give rise to severe congestive heart failure The spleen is usually not greatly infiltrated, except for the blood vessels, but exceptions to this rule do exist The Congo red test, as mentioned previously, is usually negative because the mass of amyloid is not as great as in secondary amyloidosis and because paramyloid does not absorb the dye as avidly Blind gingival biopsy, as described by Selikoff,[167] was positive in only one case in the entire series (fig 32c)

The most common cause of death in the forty-one cases that came to autopsy was cachexia, anemia, and bronchopneumonia (40 per cent) Nine patients died with uremia; one of these demonstrated not only the typical lesions of the myeloma kidney, but, in addition, a severe, focal embolic glomerulonephritis, secondary to subacute bacterial endocarditis Three died of sepsis, which was associated, in two patients, with an acute bacterial endocarditis and in the third, with a Welch bacillus wound infection Three patients died with sudden collapse for which no cause could be found One fatal case demonstrated two unusual associated complications, a pneumococcal meningitis and a ruptured abdominal aneurysm Two died with coronary arteriosclerosis and myocardial infarction and one of agranulocytosis which developed during urethane therapy Four died with congestive failure, caused by cardiac amyloidosis.

11. DIFFERENTIAL DIAGNOSIS

It is clear from this study that a given case of multiple myeloma may appear as any one of several vastly different symptom-complexes Although the classical case of myeloma is easily recognized, it must be realized that many patients do not fall easily into any stereotyped classification, and serious errors in diagnosis may result if the atypical cases are not stripped of their disguise.

By far the largest number of myeloma patients offer no diagnostic difficulties because they present with the textbook picture of the disease. Such patients are anemic, often cachectic; they suffer from severe pain due to multiple destructive lesions in the bones, and at laboratory examination, hyperglobulinemia and/or Bence Jones proteinuria, a very rapid sedimentation rate, and other phenomena of autohemagglutination are found At the same time roentgen examination of the skeleton reveals the presence of clear-cut, punched out, oval or round osteolytic areas of complete translucency, without new bone formation either in the bone itself or in the periosteum. Fractures and collapse of vertebrae are common In other cases only generalized decalcification of the bones can be detected Bence Jones proteinuria occurs in approximately 50 per cent of the cases, more commonly in those where the serum globulin is not elevated. When this remarkable protein can be found in the urine, *the diagnosis of multiple myeloma is almost certain*

Hyperglobulinemia is found in approximately 60 per cent of the patients with multiple myeloma Since serum globulins may be increased in many other diseases, the finding of hyperglobulinemia is less pathognomonic for the diagnosis of multiple myeloma than the presence of Bence Jones protein However, in many cases of myeloma, electrophoretic separation shows the presence of a sharp peak in

the beta or globulin area, a finding hardly ever seen in other diseases with hyperglobulinemia. Howe fractionation of the serum may also be of considerable help in the differential diagnosis At any rate, the presence of unexplained hyperglobulinemia is always a reason for careful examination of the bone marrow It is fortunate that the great majority of patients with multiple myeloma have either Bence Jones proteinuria or hyperglobulinemia In our series of ninety-seven cases only 12 per cent showed neither of these two abnormalities.

In all cases where differential diagnostic difficulties do arise, they are clearly resolved if myeloma cell proliferation is found in a bone marrow aspiration It should be borne in mind that the myeloma infiltration may be patchy in nature, therefore, in rare cases of multiple myeloma, bone marrow punctures may give negative results Occasionally, direct aspiration of an isolated focus of destruction, or even an open biopsy, may be necessary in order to reach a definite diagnosis

In the following diseases differential diagnostic difficulties frequently arise.

Skeletal Metastases of Carcinoma

Both multiple myeloma and metastatic carcinoma involving bone may give similar roentgenologic pictures In multiple myeloma the punched out lesions are usually more clearly demarcated and the bone involvement is usually more diffuse than is the case in metastatic carcinoma Whenever metastases are obviously osteoblastic, as in prostatic carcinoma, there is no diagnostic difficulty Even in the presence of osteolytic metastases, the differential diagnosis may frequently be made on the basis of the serum alkaline phosphatase In multiple myeloma the alkaline phosphatase is usually normal, while in metastatic carcinoma there is often sufficient osteoblastic reaction around the tumors to produce a significant elevation Bone marrow puncture, which is always necessary to exclude multiple myeloma, may occasionally reveal the presence of carcinoma cells

Postmenopausal and Senile Osteoporosis

The changes in the spine, and sometimes also in other parts of the skeleton, may be so similar in multiple myeloma to those seen in postmenopausal or senile osteoporosis that errors can be avoided only with difficulty The roentgenologic lesions in multiple myeloma may

consist solely of diffuse demineralization Compressed vertebrae in the spine of a patient with postmenopausal osteoporosis may duplicate exactly the radiologic picture seen in multiple myeloma There is, however, one important difference. The skeletal demineralization in postmenopausal osteoporosis is usually limited to spine and pelvis, whereas in most cases of myeloma the process is universal. Nevertheless, in rare cases of myeloma, the x-ray changes may be limited to the spine, as was observed in the patient reported on page 105 The finding of Bence Jones protein, hyperglobulinemia, or myeloma cells in marrow aspirate are sufficient to exclude osteoporosis

Hyperparathyroidism

In most cases of hyperparathyroidism with skeletal involvement, careful study of the roentgenograms gives important clues to the differential diagnosis. The uniform, ground-glass appearance of the skull in hyperparathyroidism is rather characteristic. Even more important are the biochemical changes of the blood serum. Although hypercalcemia occurs in both hyperparathyroidism and multiple myeloma, it is a more frequent and more marked finding in hyperparathyroidism Decrease of the inorganic phosphate and increase of the alkaline phosphatase of the serum, which are constant in hyperparathyroidism with skeletal involvement, are not found in multiple myeloma

Anemia

Every case of unexplained anemia merits a bone marrow puncture In this way, cases of multiple myeloma, in which the outstanding clinical feature is anemia, will be easily diagnosed, even if the bone lesions are not characteristic.

Lymphatic Leukemia

When the peripheral blood is invaded by large numbers of myeloma cells, that is, when plasma cell leukemia develops, differential diagnostic difficulties may arise. The myeloma cells which are found in the peripheral blood often resemble lymphocytes In such cases only an experienced hematologist may be able to recognize the foreign cells as myeloma cells. Lymphadenopathy and splenomegaly are not unusual in myeloma when plasma cell leukemia occurs. Since a bone marrow puncture should be performed in every leukemia, this differential diagnostic problem is usually easily solved.

Giant Cell Tumors

Large plasmocytomas may simulate the radiologic picture of a giant cell tumor. This holds true especially for large plasmocytomas of the pelvis. In this respect it should be repeated that giant cell tumors do not occur in flat bones. Whenever an osteolytic lesion with multiple septum formation is found in a flat bone, the presence of a plasmocytoma or a lipoid granuloma should be seriously considered, and a bone marrow puncture or even a biopsy of the tumor should be performed

When the only demonstrable lesion in myeloma occurs as a solitary focus of bone destruction without septum formation, and if the lesion is situated in the spine, there may be confusion with bone sarcoma, lipoid granuloma, or even Pott's disease. In many cases, the diagnosis can only be made by biopsy of the lesion, but it would be wise, prior to open biopsy, to examine the bone marrow in all cases with such an isolated lesion.

Albuminuria, Chronic Glomerulonephritis with or without Uremia

Unless a careful Jacobsen procedure is carried out, Bence Jones proteinuria can easily be missed when significant albuminuria coexists. The importance of the HCl ring test for screening purposes has already been emphasized Unless this test is routinely performed in all instances of albuminuria, cases of Bence Jones proteinuria are likely to go undetected. Bence Jones protein should be searched for especially in cases of "nephritis" with heavy albuminuria, but without hypertension

Cases of multiple myeloma in which an obscure type of nonhypertensive uremia is the outstanding sign often represent a most difficult diagnostic problem This uremia, caused by the myeloma kidney, may not be accompanied by bone lesions, hyperglobulinemia, or bone pain. However, every such case in our series had Bence Jones protein in the urine, and this examination should be carried out carefully in every case of renal insufficiency of unknown etiology. Otherwise, these cases may be erroneously carried for long periods of time as examples of chronic glomerulonephritis or chronic pyelonephritis.

Fever of Unknown Origin

Fever is observed in about half of the patients with multiple myeloma It occasionally happens that fever is present before the

typical signs of myeloma become evident; therefore, the possibility of *multiple myeloma should be considered* in patients with fever of unknown origin. Patients with fever due to myeloma are nearly always anemic and here again the bone marrow puncture which has to be performed for the study of the anemia will be revealing.

Back Pain

In multiple myeloma, pain in the back and ribs, often excruciating in character, is a very common finding Nevertheless, patients are encountered whose only complaint is a moderate degree of low back pain One such patient with backache was admitted to the Mount Sinai Hospital. This pain developed when he was hit by a wave while surf bathing After many variegated diagnostic procedures had given completely negative results, a bone marrow puncture at last revealed the true state of affairs

Certain myeloma cases may display an entirely normal skeleton on roentgen examination and a small number of this group may even have no bone pain. In such cases the diagnosis may not be established before autopsy, unless a marrow aspiration is made.

Hepatosplenomegaly

It should be emphasized that marked visceral involvement by myelomatous tissue, causing hepatosplenomegaly and lymphadenopathy, may produce a clinical picture easily confused with reticulum cell sarcoma or one of the other lymphomata Even with the aid of tissue sections considerable difficulty may arise in differential diagnosis in some of these cases

Paramyloidosis

When multiple myeloma is the cause of paramyloidosis the presence of myeloma is often masked by the symptoms due to widespread amyloid infiltration of the various organs *Thus, the dominant picture may be one of congestive failure due to amyloid deposition in the myocardium.* Massive gastrointestinal bleeding or intestinal obstruction is occasionally caused by intestinal paramyloidosis secondary to myeloma (p. 94). A gingival biopsy may sometimes reveal the presence of paramyloidosis and thereby point to the possibility of multiple myeloma. The presence of macroglossia is always a point in favor of this diagnosis.

Osteomalacia

Osteomalacia is so rare in this part of the world that the disease will hardly ever cause differential diagnostic difficulties. The decreased serum calcium and phosphorus, the increased serum phosphatase, and especially the hypocalciuria so characteristic of osteomalacia, are not seen in myeloma.

In this series, the diagnosis was not considered as established until it was supported by pathologic evidence, either biopsy material or bone marrow aspirate The mere presence in the marrow of an increased number of plasma cells is not sufficient evidence, although the presence of more than 10 per cent is highly suggestive of myeloma It must be emphasized that the plasma cells must be abnormal or atypical Multiple myeloma must be carefully distinguished from hypersensitivity reactions which may be associated with hyperglobulinemia and plasmocytosis of the marrow We have seen as many as 12 per cent mature plasma cells in a case of Hodgkin's disease and 19 per cent in a case of lymphopathia venereum In cases of agranulocytosis the number of plasma cells often exceed that of the other bone marrow elements

12. TREATMENT OF MYELOMA

Many different therapeutic methods have been tried, but none of these have shown evidence of being able to *cure* multiple myeloma In fact, despite one hundred years of intensive study, we are little closer to the cure of multiple myeloma than was Dr. Watson, in 1848, when he administered "steel and quinine"[116] On the other hand, there are available several physical and chemical agents which, in occasional cases, can produce remissions of pain and effect other signs of improvement, indicating that the course of the disease has been halted at least temporarily.

Radiotherapy

Despite the fact that multiple myeloma is not a very radiosensitive disease, radiotherapy is still the most commonly employed therapeutic agent It is mainly of use in the palliative treatment of a localized plasmocytoma causing pain or exerting pressure on adjacent structures. The benefits, which may be expected are well exemplified by the patient H C. described on page 45 In such cases the results, at least for a time, are good. Recalcification of the local lesion may occur (fig 41), but no proven cures have been reported In those cases with spinal cord compression and resultant paresis or paraplegia, laminectomy and radiotherapy give considerable relief, as in the case of J. W , described on page 33. Jacox and Kahn[86] and Batts[16] have emphasized the value of laminectomy and subsequent radiotherapy in such cases, both in the alleviation of neurologic symptoms and in the prolongation of life Garland and Kennedy[65] reported, in a group of patients treated with radiotherapy, a survival period of twenty-three months, as opposed to a survival period of twelve months in a comparable untreated group. However, one of their patients survived for

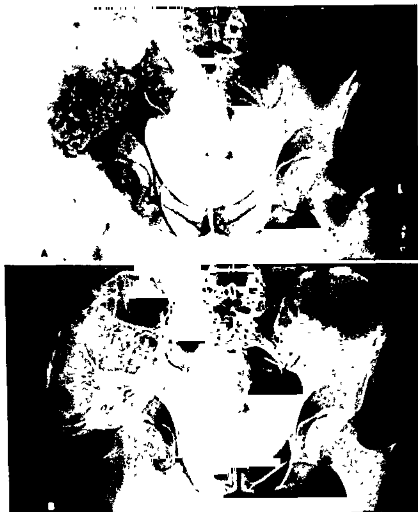


Fig 41 —Huge myelomatous tumor of ilium (*a*) Before radiotherapy (*b*) After radiotherapy Note the recalcification of the remaining specules of bone in the lesion following treatment

fourteen years, which helped to weight the statistics heavily in favor of the treated group In cases with diffuse or universal bone lesions, spray irradiation to the entire body may be used The results are often discouraging, but, in an occasional case, relief of pain is obtained

Therapeutic trials with radioactive phosphorus have been reported

12. TREATMENT OF MYELOMA

Many different therapeutic methods have been tried, but *none of these have shown evidence of being able to cure* multiple myeloma In fact, despite one hundred years of intensive study, we are little closer to the cure of multiple myeloma than was Dr. Watson, in 1848, when he administered "steel and quinine "[116] *On the other hand, there are available several physical* and chemical agents which, in occasional cases, can produce remissions of pain and effect other signs of improvement, indicating that the course of the disease has been halted at least temporarily.

Radiotherapy

Despite the fact that multiple myeloma is not a very radiosensitive disease, radiotherapy is still the most commonly employed therapeutic agent. It is mainly of use in the palliative treatment of a localized plasmocytoma causing pain or exerting pressure on adjacent structures. The benefits, which may be expected are well exemplified by the patient H. C. described on page 45 In such cases the results, at least for a time, are good Recalcification of the local lesion may occur (fig. 41), but no proven cures have been reported. In those cases with spinal cord compression and resultant paresis or paraplegia, laminectomy and radiotherapy give considerable relief, as in the case of J. W., described on page 33. Jacox and Kahn[86] and Batts[18] have emphasized the value of *laminectomy and subsequent radiotherapy in* such cases, both in the alleviation of neurologic symptoms and in the prolongation of life. Garland and Kennedy[65] reported, in a group of patients treated with radiotherapy, a survival period of twenty-three *months,* as opposed to a survival period of twelve months in a comparable untreated group However, one of their patients survived for

5 per cent glucose in distilled water. An average of fifteen to twenty injections are given.

Sometimes the effect of stilbamidine is very satisfactory indeed, as illustrated by the following four case histories.

The first myeloma patient treated with stilbamidine, a 59 year old male, was completely incapacitated by severe bone pains on admission X-ray examination showed the presence of numerous small foci of rarefaction throughout the calvarium Osteolytic lesions were also seen in the upper ends of the tibiae and the upper and lower ends of the femora No Bence Jones protein was found in the urine and the globulin content of the serum was normal Sternal marrow aspiration revealed the presence of 30 per cent myeloma cells In February 1945 he received a series of stilbamidine injections totalling 2 5 Gm After the treatment, he felt entirely well. He resumed his activities as a hospital porter, carried heavy burdens on his shoulders and lived lustily, even drinking quite heavily Not until 1949, four years later, did he start to lose weight Anorexia was noted and he developed pain in the buttocks At that time the liver and spleen were found to be enlarged to about 6 cm below the costal margin Bence Jones protein was still absent, but a marked hyperglobulinemia of 7 Gm per cent had developed, consisting mainly of alpha globulin (table 5) The bone marrow picture was again typical for myeloma Osteolytic lesions, compatible with the diagnosis of multiple myeloma, were found on the roentgenograms of femora, tibiae, fibulae, and astragali He responded favorably to a new series of stilbamidine injections, but relapsed again shortly thereafter Trials with other antimyeloma medications were without avail He developed plasma cell leukemia and expired in April 1950, more than five years after the first course of stilbamidine had been administered Autopsy examination revealed widespread myeloma of the bones and infiltration of the viscera with myeloma cells

The second patient, a 61 year old female with widespread roentgenologic lesions, had been bedridden for several months with excruciating bone pains There was no Bence Jones proteinuria and the globulin of the serum was normal (1 6 Gm per cent) The bone marrow smears were typical for myeloma In April 1945 she received stilbamidine injections to a total of 1 175 Gm During [illegible]

Bence Jones proteinuria was still absent and the serum globulin was only 1.3 Gm per cent She received at this time 2 8 Gm of stilbamidine, followed by 1 Gm of pentamidine, but she did not improve The serum globulin remained normal (1 2 Gm per cent) until she ultimately died in June 1947 In this case also, the clinical improvement after stilbamidine treatment was gratifying, at least temporarily

A third patient, a 58 year old woman with widespread bone lesions, had been bedridden for several months because of several bone pains Bence Jones proteinuria was absent but the serum globulin was increased to 4.4 Gm per cent Bone marrow smears revealed the typical picture of multiple myeloma In June 1948 she was given a course of 2.4 Gm of 2-hydroxystilbamidine in

by several observers.[75,112,147,207] All of them agree that results are discouraging, although an occasional patient may have temporary relief of pain. Reinhard and his associates[147] *have even felt that the* duration of life in two of their patients was actually shortened by the leukopenia and thrombopenia produced by the medication Hall and Watkins[75] report one case in which the therapeutic benefit obtained by combined use of radiophosphorus and x-ray therapy was greater than could be expected from either treatment alone. Radioactive strontium has also been tried with inconclusive results[19]

Stilbamidine and Other Diamidines

The *renewed interest in a chemotherapeutic approach to the* treatment of multiple myeloma originated in 1946 At that time it was reported that stilbamidine (diamidino-stilbene) had a favorable *effect on the bone pains of myeloma patients*[174,175,182] *Another closely* related compound, pentamidine, (diamidino-dibenzopentane) produced a similar symptomatic improvement. It was stressed in the first report and repeated in later publications that these compounds did not cure the disease and did not influence hyperglobulinemia or Bence Jones proteinuria, when present.

Stilbamidine and pentamidine have been employed successfully since 1939 for the treatment of kala azar. These compounds have proved to be effective even in patients who were refractory to antimony treatment[2] In order to avoid confusion, it should be stressed that neither stilbamidine nor pentamidine contains antimony.

The possibility that stilbamidine might affect the course of multiple myeloma was entertained in part because hyperglobulinemia, a constant finding in kala azar, is also found in 60 per cent of the cases of multiple myeloma. There was, however, another reason why this investigation was initiated The cytoplasm of myeloma cells, if stained with Giemsa or other Romanowsky stains, is deeply basophilic; if stained with pyronin, strongly pyroninophilic. The basophilia and pyroninophilia of the cytoplasm of the myeloma cells indicate the presence of large amounts of ribosenucleic acid.[29] Since stilbamidine and other diamidines in high dilutions are capable of precipitating nucleic acid[91] it seemed worthwhile to study the effect of these drugs on the nucleoproteins of myeloma cells.

Stilbamidine is injected intravenously in the form of stilbamidine di-isethionate, in daily doses of 100 to 150 mg dissolved in 200 cc. of

porarily, more dramatic. As will be explained later, urethane in some cases actually influences hyperglobulinemia and Bence Jones proteinuria. Stilbamidine, moreover, has several unfortunate side effects apart from transient hypotension which appears after intravenous injection. Whereas stilbamidine in therapeutic doses does not noticeably affect the function of the healthy kidney, it seems to influence adversely the function of previously damaged kidneys.[9,121] It has already been mentioned that a significant number of myeloma patients either have myeloma kidneys or actually suffer from a diffuse glomerulonephritis. This greatly limits the number of myeloma patients who may be considered for stilbamidine treatment. The greatest disadvantage of stilbamidine consists of an especially disagreeable and annoying side effect. Two to three months after the institution of stilbamidine treatment a dissociated neuropathy of the trigeminal area may develop.[38,73,166,168,174,175] This consists of anesthesia to touch in one or all the branches of the trigeminal nerve, but no loss of pain or temperature sensation. Subjectively the patients complain of a "wooden face," usually associated with tingling and burning, which is especially troublesome when it affects the eyelids and the forehead. These extremely disagreeable paresthesias develop a few months after termination of the treatment, even if the total dose of stilbamidine has not exceeded ten injections of 150 mg. In general, it appears that the larger the total dose given, the more intense the trigeminal disturbance. In many patients the paresthesias persist for months, in exceptional cases even for years. This neuropathy is so disabling that stilbamidine has been replaced by pentamidine in the treatment of kala azar. As will be pointed out later, it may be possible to diminish the intensity of the neuropathy by protecting patients from sunlight for several months after stilbamidine treatment has been terminated.

Notwithstanding all the disadvantages mentioned above, the stilbamidine treatment of multiple myeloma captivated the interest of many clinicians because it was possible to demonstrate that this compound combined with the nucleoproteins of the cytoplasm of the myeloma cells. In many patients it was found that following stilbamidine treatment dark basophilic and pyroninophilic granules developed in the cytoplasm of alcohol fixed myeloma cells[181,182] (frontispiece—fig. 3d). The properties of these granules indicate that they consist, for the greater part, of ribosenucleic acid. That the granules can be dissolved by the enzymatic activity of ribonuclease

divided daily doses She responded favorably and was able to resume her normal activities She then received one injection of 2-hydroxystilbamidine per week for six months and did well thereafter This favorable condition persisted for about one year until June 1949 when she developed a relapse The serum globulin was now 4 6 Gm per cent and about 50 per cent of the total serum protein consisted of beta globulin (table 7, case 5). A new series of 2-hydroxystilbamidine injections totalling 2 0 Gm did not relieve her pain. In December 1949 *urethane treatment was started which soon resulted in thrombopenia and* a general hemorrhagic tendency She received ACTH, cortisone, and small doses of urethane intermittently but died after long suffering in December 1951

A fourth patient, who has seemingly profited considerably from stilbamidine treatment, has already been mentioned (p 14) She died more than eight years after the first series of stilbamidine injections was given

These four favorable cases are chosen from sixty patients treated with stilbamidine or other diamidine derivatives. In most myeloma patients, the improvement resulting from such treatment was of much shorter duration or was absent It was impossible to predict in advance which patients would profit from stilbamidine or which cases would be resistant Since 1946 a number of reports have been published indicating that other clinicians have also observed more or less favorable effects of stilbamidine and pentamidine upon the course of multiple myeloma [25,73,77,145,165] Some authors have had completely negative results Although we have never observed a decrease of the hyperglobulinemia or Bence Jones proteinuria under the influence of stilbamidine, others have reported, in a few instances, not only clinical improvement but also a decrease of the hyperglobulinemia [143 213] The Medical Division of Merck and Company, which for several years dispensed stilbamidine free for clinical trials, summarized, in 1948, one hundred and ninety-four cases of multiple myeloma, treated with this compound by one hundred and fifty different groups of clinicians [128] More than half of these patients received, temporarily, either partial or complete relief from the severe bone pains which are associated with this disease Some of the patients experienced dramatic benefit

There are several reasons, however, why stilbamidine has lost a good deal of its popularity in the treatment of multiple myeloma Urethane, which has more recently been recommended for the treatment of this disease, can be administered orally. This is a great advantage, especially since the intravenous injections of stilbamidine must be given very carefully in order to avoid obliteration of veins In addition, the results of urethane treatment may be, at least tem-

like stilbamidine, this 2-hydroxy derivative destroys kala azar flagellates in the test tube and in the experimental animal [62] It was demonstrated that the administration of 2-hydroxystilbamidine to patients did not further impair the function of the myeloma kidney and that it did not cause a trigeminal neuropathy [178,179,184] A possible explanation for the latter difference may be connected with the light sensitivity of stilbamidine. Stilbamidine is converted, under the influence of ultraviolet light, to a toxic compound When exposed to the sunlight, a stilbamidine solution readily loses its fluorescence, whereas under the same conditions 2-hydroxystilbamidine remains essentially unchanged [184] It thus seems possible that stilbamidine, deposited in the skin, slowly changes to a toxic substance under influence of sunlight and that the latter product causes the trigeminal neuropathy It should be pointed out that in this part of the world the neuropathy is limited to the trigeminal area In the tropics, the arms and chest, which are usually uncovered, are also involved

This 2-hydroxystilbamidine is usually administered intravenously, dissolved in 5 per cent glucose in distilled water It can however, if necessary, be injected intramuscularly In many respects the actions of 2-hydroxystilbamidine and of stilbamidine are identical In patients with kala azar,[169] South American mucocutaneous leishmaniasis,[179] and visceral blastomycosis,[184] the results of 2-hydroxystilbamidine therapy are highly satisfactory After intravenous administration of 2-hydroxystilbamidine, basophilic granules can also be demonstrated in alcohol-fixed myeloma cells These granules consist of ribosenucleic acid combined with 2-hydroxystilbamidine. The same holds true for cells of other organs. More important still, unlike stilbamidine, considerable quantities of 2-hydroxystilbamidine can be visualized, not only in the cytoplasm, but also in the nuclei of myeloma cells and of cells of parenchymatous organs.[180,183,185] Bone pains are ameliorated, in at least some myeloma patients, by the 2-hydroxy compound However, just as when treated by stilbamidine, the disease process appears unaltered and no clear cut influence of the hydroxy compound upon the hyperglobulinemia or the Bence Jones proteinuria has been observed

Urethane

In recent years it has been shown that urethane, which can be administered orally, has a temporary salutary effect upon the pain and other clinical manifestations of multiple myeloma

is strong evidence for this identity[182] In addition, photographs made with a quartz microscope and using ultraviolet light of various wave lengths reveal that the granules absorb light of 2570 Angstrom units, the characteristic wave length for nucleic acid.[181–185] It was further shown that the granules contain not only ribosenucleic acid, but also stilbamidine When studied with the fluoroscent microscope, they show a fluorescence similar to that of pure stilbamidine in crystalline form or in solution Moreover, when studied with the quartz microscope, the granules absorb light of 3300 Angstrom units, which is characteristic for stilbamidine[183]

Thus, part of the stilbamidine administered to myeloma patients is found in the bone marrow and, at least after fixation with methyl alcohol, it was found within the myeloma cells, evidently conjugated with ribosenucleic acid This, however, is not a specific characteristic of myeloma cells. In many other cells, for example liver cells, preformed ribosenucleic acid granules are present After stilbamidine treatment, these nucleoprotein granules of liver cells become much larger than before and can be demonstrated to contain some of the injected diamidine Kurnick and his associates observed that after injections of stilbamidine, granules consisting of ribosenucleic acid and stilbamidine developed in the tumor cells of mice with a transplantable ascites tumor[99] The presence of these granules, however, did not influence the growth of the tumor

Only 10 per cent of the injected stilbamidine is excreted in the urine[159] Chemical determinations have demonstrated that after stilbamidine injections, considerable quantities of the diamidine are deposited in various organs, especially in the liver, kidneys, and adrenals The diamidine remains there for many months, even years.[180] This deposition varies to some extent in different species In humans, the stilbamidine concentration is highest in the liver and adrenals, lower in the kidneys. In the mouse, on the other hand, the largest concentration is found in the kidneys. Thus it has become apparent that pharmacologically the diamidines are remarkable substances.

Because of the toxic side effects of stilbamidine, other diamidine derivatives have been sought which would not further impair the function of an already damaged kidney and which also would not produce the very annoying trigeminal neuropathy. One of these derivatives, 2-hydroxystilbamidine, apparently fulfills these requirements. It has been established from animal experiments that,

number of abnormal plasma cells in the bone marrow were observed together with morphologic changes in the plasma cells which indicated arrested or retarded growth. Some patients, who had been bedridden before treatment, improved so much that they became ambulatory and could resume part of their normal activities After four to six months, roentgenologic examination revealed recalcification and reappearance of trabecular patterns in the osteolytic areas, particularly in the bones subject to weight bearing. In most instances, the skull lesions did not show actual signs of healing, but during the period of observation the progression of these lesions seemed to be checked Relapses, however, did occur.

Rundles and his associates have performed many painstaking investigations in order to explore the therapeutic efficiency of urethane in multiple myeloma [155,156] Seven of eleven myeloma patients in their series had hyperproteinemia [155] In six of these seven cases, the electrophoretic pattern revealed the presence of large amounts of gamma globulin In the seventh case the abnormal protein migrated, on electrophoresis, with a speed intermediate between the beta and gamma globulin fractions. In five patients the abnormal proteins in the serum were markedly reduced by the administration of urethane. The change in the serum proteins appeared only after urethane had been administered for at least one month and only after the growth of plasma cells, as studied by multiple bone marrow punctures, had been suppressed As the abnormal globulins disappeared from the serum, the initial low level of serum albumin rose to normal Nevertheless, a completely normal electrophoretic pattern was not restored in any of the cases. In two patients in whom plasma cell proliferation was not appreciably influenced by urethane treatment, no change in the electrophoretic pattern was observed As the concentration of the abnormal globulins of the serum was reduced, the authors reported that the Bence Jones proteinuria invariably diminished in intensity. In one of Rundles' patients with extreme skeletal disease and marked Bence Jones proteinuria, hypoproteinemia existed, but the electrophoretic pattern was practically normal Following urethane treatment, the proteinuria became much less and the concentration of the total protein of the serum rose to normal. Thus, it seemed that as the growth of plasma cells was retarded or arrested by the administration of urethane, abnormal serum and urinary proteins tended to return to normal

Rundles and his associates have postulated that during treatment

The fact that urethane is a protoplasmic and mitotic poison has been known for many decades As far back as 1910, Warburg[208] demonstrated that the addition of 1 Gm. of phenylurethane to 2 liters of sea water suppressed the cell division and nuclear division of sea urchin eggs. Urethane has been shown to inhibit the development of leukemia and the growth of certain tumors. Paradoxically enough, urethane not only inhibits mitoses, but it also produces, after a long latent period, pulmonary tumors in mice and rats There is no parallelism between the antimitotic effect and the carcinogenic and antileukemic actions of the drug, since they occur at totally different time-dose-response relationships.

As a result of experimental work on animals with transplantable leukemia, ethyl urethane was administered to a large number of patients suffering from leukemia and other malignancies It is now generally agreed that in chronic myelogenous leukemia the action of urethane is comparable to, though possibly not as consistently effective as, roentgen radiation.[138a] Urethane is fairly effective in chronic lymphatic leukemia, but almost completely valueless in the acute forms of the disease

Since multiple myeloma can be considered to represent the aleukemic form of plasma cell leukemia, it was only natural that clinicians would be interested in the influence of urethane upon the course of myeloma Alwall[6] was the first to report favorable effects of urethane upon multiple myeloma. His first patient, suffering chiefly from skeletal pain, showed no improvement during the administration of 3 to 4 Gm of urethane daily for four months A gratifying result was later obtained, however, by intravenous injections of stilbamidine A second patient with multiple myeloma and severe anemia was also given urethane in doses of 3 to 4 Gm daily. During the first four months of the treatment, anemia, increased sedimentation rate, albuminuria, and hyperglobulinemia were all favorably influenced. Plasma cells disappeared from the bone marrow. This remission was sustained for three years and then a relapse occurred which caused the death of the patient about four years after the treatment had been started.[201]

In 1949, Loge and Rundles[109] confirmed Alwall's findings. They administered 2 to 4 Gm. of urethane per day and continued this over a period of eight to ten weeks. A total dose varying between 120 and 300 Gm. appeared necessary to obtain a favorable result Under this treatment, fever and pain often abated and striking reductions in the

treatment was continued every other month without interruption Despite the pain, he was in relatively good condition and could still continue his usual activities For another five months his weight and blood picture were well maintained but in January 1951 his condition rapidly deteriorated He was [illegible]

a complete sensory and motor paralysis of the lower extremities and bowel and bladder incontinence. A destructive process was visualized on the roentgenograms, involving portions of the bodies, laminae, and pedicles of the third, fourth, and fifth dorsal spines He died in March 1951, about one year and nine months after the disease was first diagnosed. The autopsy revealed the presence of many myelomas of the skull, compression of the cord by collapse of the second and third dorsal vertebrae, involvement of the right eighth rib and first left rib and practically all the bodies of the thoracic and lumbar vertebrae There was myelomatous infiltration of the liver and parenchymatous nephritis

In this patient, urethane apparently improved the general condition and reduced the high serum globulin to normal values (table 14). The duration of the disease was evidently not changed, since the average span of life of a patient with multiple myeloma, after the disease has been diagnosed, usually varies between one and a half to two years It should also be considered that before the urethane treatment was started the outstanding symptoms and signs of this patient consisted of fatigue, anemia, and hyperglobulinemia, but that actual bone pains or x-ray lesions were not present.

TABLE 14 —*Mr. B —Multiple Myeloma. Urethane Treatment Subjective Improvement for One Year with Reduction of Hyperglobulinemia to Normal Values Exitus Twenty-One Months after Start of Urethane Administration*

Date	Hgb (Gm. %)	Alb /glob	Bence Jones protein	Urethane
6/21/49	9	3 8/11 2	One plus	Started
11/18/49	14.0	5 4/2 9	Neg	270 Gm
11/10/50	6	4 9/3 3	Neg	630 Gm
March '51	Died			

A second patient was seen in November 1948 after a sudden onset of low back pain with spasm and restriction of motion Roentgenograms made at that time revealed no lesions In March 1949, the pain became much worse and the roentgenograms now showed punched-out areas in many bones, most marked in the lower ribs and pelvis The hemoglobin was 78 per cent; the blood urea nitrogen, serum calcium, phosphorus, and phosphatase were all within normal limits The albumin content of the serum was 3 Gm. per cent, the globulin

on page 104. Moderate leukopenia always develops during urethane treatment, but as a rule this does not necessitate discontinuing therapy. In one patient a severe agranulocytosis developed, the white count decreasing to 800 cells per cu. mm. Thrombopenia with hemorrhagic tendency is also not rare. All five patients who responded temporarily to urethane ultimately died with no noticeable increase in longevity.

Whereas the effect of urethane treatment in multiple myeloma in hospitalized patients was not encouraging, temporarily favorable results were occasionally obtained in patients who were seen on an out patient basis.

A 55 year old man was first seen on June 21, 1949 He complained that in the past year he had lost 20 pounds in weight and that in the past six months he had become very weak Six weeks prior to the first examination he had an episode of "virus pneumonia " After this acute illness the fatigue became much more severe and profuse sweating was noted There were no complaints of pain. The physical examination was entirely negative except for moderate pallor of the skin and conjunctivae The patient was anemic with 9 Gm of hemoglobin, and 2,540,000 red cells There were 5500 white cells with a normal distribution One plus Bence Jones protein was found in the urine The sedimentation rate was markedly increased to 34 mm in 45 minutes (Cutler method) The blood urea nitrogen was 18 5 mg per cent, uric acid 5 4 mg per cent, creatinine 1 6 mg per cent, serum calcium 16 4 mg per cent *The total protein content* of the serum was 15 Gm per cent with 3 8 Gm per cent albumin and 11 2 Gm per cent globulin Sternal marrow aspiration showed that the bone marrow contained 95 per cent young myeloma cells The patient was started on urethane therapy, 5 Gm daily His general condition improved rapidly, the red blood cells rose to 4,500,000, the hemoglobin to 12 Gm per cent After he had received 210 Gm of urethane in the course of six weeks, the daily dose was *reduced to 2 Gm , given during alternate months His weight rose to* 225 pounds, he was completely free of symptoms, and he returned to an active business life During the month in which he received urethane, the white blood cells dropped to 2500 per cu mm only to rise again to 4000 per cu mm during the month when no urethane was given On November 18, 1949, about four months after the urethane treatment had been started, the patient [illegible] content of the serum had improved [illegible] Gm [illegible] a had [illegible] With urethane being administered every other month, he remained well until September 1950 when he began to complain of pains in the right lower chest [illegible]

improved again. Between October 1951 and June 1952 he had taken another 240 Gm of urethane Nevertheless, as shown by roentgen examination, the disease continued to spread and the hyperglobulinemia persisted The serum albumin was 4 1 Gm per cent, and the serum globulin 5 4 Gm per cent.

In this patient the disease was apparently controlled during the first period of treatment and the hyperglobulinemia disappeared Two years and five months later a relapse occurred This was controlled clinically by renewed treatment with urethane. Nevertheless, roentgenologic study during the subsequent period of apparent well-being showed that the myeloma was rapidly spreading throughout the skeleton and the hyperglobulinemia, which had recurred during the relapse, persisted (table 15).

A third patient who responded temporarily to urethane treatment complained chiefly of pain in the lower back Roentgenograms showed marked destruction of the fifth lumbar vertebra There were also a few osteolytic lesions in the rest of the skeleton and the bone marrow showed the presence of a large number of myeloma cells This patient was treated with urethane and roentgen therapy The pains in the back disappeared rapidly and recalcification of the partially destroyed fifth lumbar vertebra was noted One year after the beginning of the treatment, the roentgenograms of the spine showed that a considerable improvement had been obtained (fig 42) However, during the same period, new myelomatous lesions had started to develop in the skull (fig 43) and in the rest of the skeleton Despite continued urethane treatment, roentgen treatment, cortisone, and ACTH, the disease was rapidly progressive and the patient succumbed one year and eight months after the disease was first discovered

It is discouraging that in the large number of patients we have seen, only three cases showed a favorable response to urethane These three cases seem to confirm the observations of Rundles and his associates that in certain patients urethane has an inhibitory influence upon the progress of multiple myeloma This drug occasionally halts the proliferation of the myeloma cells and, as a result, the hyperglobulinemia may temporarily disappear In some cases, the total serum protein diminishes, and the hyperglobulinemia as determined by Howe fractionation seems to be reduced However, electrophoretic analysis may show that the relative proportion of the abnormal globulin fractions does not change (table 7, case 1) The favorable influence, moreover, is transient and in most cases where improvement is obtained, the life expectancy does not seem to be longer than the average, that is, about one and a half to two years after the onset of the disease An occasional patient may live longer than two years, but even without treatment, this does occur As mentioned above,

TABLE 15—*Mr L.—Multiple Myeloma, Urethane Treatment Subjective Improvement for Three and One Half Years, but Nevertheless with Roentgenologic Evidence of Progress of the Disease*

Date	Hgb. (%)	Alb /glob	Bence Jones protein	Urethane
March '49	78	3 0/5 0	Neg	Started
June '49	80	4 3/2 0	Neg	490 Gm
Dec '50	—	3 9/1 5	Neg	630 Gm
Aug '51	—	4 3/4 7	Neg	630 Gm
Sept '51	72	5 2/3 2	Neg	660 Gm.
Dec '51	68	5 1/3 0	Neg	660 Gm
June '52	70	4 1/5 4	Neg	900 Gm

content 5 Gm per cent, the sedimentation rate was very much increased. No Bence Jones protein was found in the urine A sternal marrow puncture showed that 80 per cent of the marrow cells were replaced by plasma cells. Urethane treatment was started on March 31, 1949. For two days a daily dose of 2 Gm was given, thereafter 4 Gm were administered daily. He rapidly improved and after three months of treatment, the albumin content of the serum had increased to 4 3 Gm per cent and the globulin content had decreased to 2 Gm per cent (table 15) In July he returned to work On August 20, 1949, urethane was stopped because the white blood cells had fallen to 1700 per cu mm Up to this point he had received a total of 580 Gm of urethane. The patient was on a full working schedule The hemoglobin was maintained at 80 per cent and the red blood count ranged around 4,000,000. Beginning in September 1949, 25 mg. of testosterone propionate were administered twice weekly by intramuscular injection In November, urethane therapy was resumed at a daily dose of 2 Gm Urethane was stopped in December after an extra 50 Gm of the drug had been taken

One year later, in December 1950, the serum albumin was 3 9 Gm per cent, the serum globulin 1.5 Gm. per cent Except for various minor migratory pains, the patient's condition remained good throughout this period and he worked regularly He continued to do well and therefore did not take any urethane until August 11, 1951, when a severe attack of pain in the lumbar spine occurred At this time, the total protein was 9.0 Gm per cent with 4 3 Gm per cent albumin and 4 7 Gm per cent of globulin. It was evident that the [illegible]

proved. In the middle of October, the patient complained again of bone pains Urethane therapy was resumed, 2 Gm daily. His complaints of bone pain persisted for another month but then gradually improved. He continued the urethane treatment 2 Gm. daily on alternate months, and in June 1952 he felt

improved again Between October 1951 and June 1952 he had taken another 240 Gm of urethane Nevertheless, as shown by roentgen examination, the disease continued to spread and the hyperglobulinemia persisted The serum albumin was 4 1 Gm per cent, and the serum globulin 5.4 Gm per cent.

In this patient the disease was apparently controlled during the first period of treatment and the hyperglobulinemia disappeared Two years and five months later a relapse occurred This was controlled clinically by renewed treatment with urethane. Nevertheless, roentgenologic study during the subsequent period of apparent well-being showed that the myeloma was rapidly spreading throughout the skeleton and the hyperglobulinemia, which had recurred during the relapse, persisted (table 15).

A third patient who responded temporarily to urethane treatment complained chiefly of pain in the lower back Roentgenograms showed marked destruction of the fifth lumbar vertebra There were also a few osteolytic lesions in the rest of the skeleton and the bone marrow showed the presence of a large number of myeloma cells This patient was treated with urethane and roentgen therapy The pains in the back disappeared rapidly and recalcification of the partially destroyed fifth lumbar vertebra was noted One year after [illegible]

[illegible]

gen treatment, cortisone, and ACTH, the disease was rapidly progressive and the patient succumbed one year and eight months after the disease was first discovered

It is discouraging that in the large number of patients we have seen, only three cases showed a favorable response to urethane These three cases seem to confirm the observations of Rundles and his associates that in certain patients urethane has an inhibitory influence upon the progress of multiple myeloma This drug occasionally halts the proliferation of the myeloma cells and, as a result, the hyperglobulinemia may temporarily disappear In some cases, the total serum protein diminishes, and the hyperglobulinemia as determined by Howe fractionation seems to be reduced However, electrophoretic analysis may show that the relative proportion of the abnormal globulin fractions does not change (table 7, case 1) The favorable influence, moreover, is transient and in most cases where improvement is obtained, the life expectancy does not seem to be longer than the average, that is, about one and a half to two years after the onset of the disease An occasional patient may live longer than two years, but even without treatment, this does occur. As mentioned above,

TABLE 15.—*Mr. L—Multiple Myeloma. Urethane Treatment. Subjective Improvement for Three and One Half Years, but Nevertheless with Roentgenologic Evidence of Progress of the Disease*

Date	Hgb (%)	Alb /glob	Bence Jones protein	Urethane
March '49	78	3 0/5 0	Neg	Started
June '49	80	4 3/2 0	Neg.	490 Gm
Dec '50	—	3 9/1 5	Neg.	630 Gm
Aug '51	—	4 3/4 7	Neg	630 Gm
Sept '51	72	5 2/3 2	Neg	660 Gm
Dec '51	68	5 1/3 0	Neg.	660 Gm.
June '52	70	4 1/5 4	Neg	900 Gm.

content 5 Gm per cent, the sedimentation rate was very much increased. No Bence Jones protein was found in the urine A sternal marrow puncture showed that 80 per cent of the marrow cells were replaced by plasma cells Urethane treatment was started on March 31, 1949 For two days a daily dose of 2 Gm was given, thereafter 4 Gm were administered daily. He rapidly improved and after three months of treatment, the albumin content of the serum had increased to 4 3 Gm per cent and the globulin content had decreased to 2 Gm per cent (table 15) In July he returned to work On August 20, 1949, urethane was stopped because the white blood cells had fallen to 1700 per cu. mm Up to this point he had received a total of 580 Gm of urethane. The patient was on a full working schedule The hemoglobin was maintained at 80 per cent and the red blood count ranged around 4,000,000. Beginning in September 1949, 25 mg of testosterone propionate were administered twice weekly by intramuscular injection. In November, urethane therapy was resumed at a daily dose of 2 Gm Urethane was stopped in December after an extra 50 Gm of the drug had been taken

One year later, in December 1950, the serum albumin was 3 9 Gm per cent, the serum globulin 1 5 Gm per cent. Except for various minor migratory pains, the patient's condition remained good throughout this period and he worked regularly He continued to do well and therefore did not take any urethane until August 11, 1951, when a severe attack of pain in the lumbar [illegible]

sisted for another month but then gradually improved He continued the urethane treatment 2 Gm daily on alternate months, and in June 1952 he felt

patients treated with stilbamidine, in whom the protein metabolism is not influenced as favorably as it is by urethane, may occasionally live much longer than the average of two years

In summary, urethane should be tried in patients with multiple myeloma in daily doses of 2 to 5 Gm until a total dose of 240 to 300 Gm. has been reached. A large number of myeloma patients do

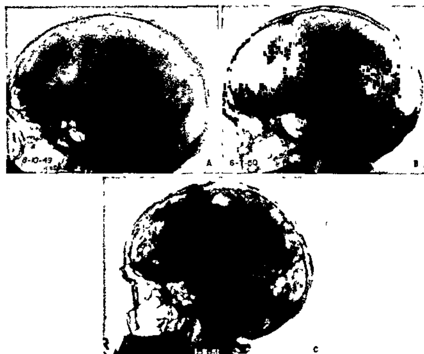


FIG 43 —Same patient as figure 42 While the lesion of the vertebra was regressing, the skull demonstrated rapidly advancing destruction

not tolerate urethane in the doses which are necessary to obtain even a temporary improvement The favorable results to be expected in patients who improve on urethane are 1) increase in the hemoglobin and a decrease in the plasma cell infiltration of the bone marrow, 2) return to normal of the hyperglobulinemia, hypoalbuminemia, and abnormal electrophoretic pattern and a decrease in Bence Jones proteinuria, 3) increase in bone density on roentgenograms and recalcification of osteolytic areas

It may be of some clinical importance that the favorable responses

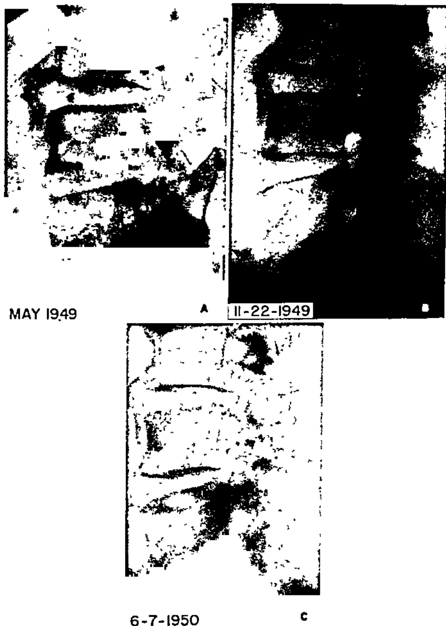


FIG 42—Apparent healing of fifth lumbar vertebral body in myeloma during therapy with urethane

patients treated with stilbamidine, in whom the protein metabolism is not influenced as favorably as it is by urethane, may occasionally live much longer than the average of two years.

In summary, urethane should be tried in patients with multiple myeloma in daily doses of 2 to 5 Gm until a total dose of 240 to 300 Gm. has been reached A large number of myeloma patients do

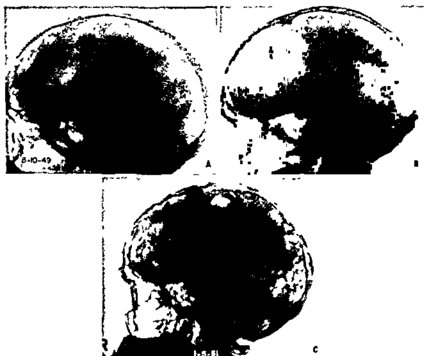


FIG 43 —Same patient as figure 42 While the lesion of the vertebra was regressing, the skull demonstrated rapidly advancing destruction

not tolerate urethane in the doses which are necessary to obtain even a temporary improvement The favorable results to be expected in patients who improve on urethane are 1) increase in the hemoglobin and a decrease in the plasma cell infiltration of the bone marrow; 2) return to normal of the hyperglobulinemia, hypoalbuminemia, and abnormal electrophoretic pattern and a decrease in Bence Jones proteinuria, 3) increase in bone density on roentgenograms and recalcification of osteolytic areas

It may be of some clinical importance that the favorable responses

to urethane which we observed were not found in patients on the hospital wards In general, patients seen on an out patient basis suffer from less advanced stages of the disease than patients admitted to the wards. It seems probable that more favorable, though still temporary responses, can be expected in the initial stages of the disease. As a matter of fact, Rundles and his associates also mention that about one third of their recent patients were referred for diagnosis and treatment so late in the course of their disease that "effective" therapy was not possible.[155,158] If the treatment is effective in the early stages of the disease, then occasionally a patient must be encountered whose span of life will exceed that of the customary two year period. The fact that one patient with multiple plasmocytomas without generalized marrow involvement (p 103) improved for a long period on urethane suggests that this form of myeloma, despite the severe nature of the pains, may represent the initial stage of the disease.

ACTH and Cortisone

Shortly after the introduction of ACTH and cortisone into clinical medicine, Thorn[193] reported that ACTH had favorably influenced the course of one case of multiple myeloma. This patient with widespread disease improved rapidly on ACTH given in doses of 20 mg every six hours over a period of twenty days. The elevated serum globulin fell from 10 2 Gm to 4 8 Gm per 100 cc , the myeloma cells disappeared from the bone marrow, the serum calcium fell from 26 mg per cent to 10 8 mg per cent and the alkaline phosphatase of the serum rose from 3 0 to 6.8 Bodansky units per 100 cc.

The results reported by other authors have been partly good and partly bad Bethel[24] reported on eight cases of myeloma treated with ACTH and cortisone or both He observed diminution of pain, increase of appetite, and a drop of the abnormal serum globulins of at least 2 Gm per cent in four of the cases. In one patient, whose globulin fraction dropped 5.9 Gm. per cent, consecutive bone marrow smears revealed a considerable reduction in the number of myeloma cells. In the other seven patients, however, no effect upon the myeloma cells or upon the radiologic skeletal lesions could be observed. Bethel concluded that since considerable clinical and laboratory improvement had been observed in four of his eight patients, ACTH and cortisone may have a favorable, though temporary, effect upon myeloma.

Engle[57] administered 80 mg of ACTH intramuscularly for thirty-two days and 60 mg for twenty-eight days to one patient This patient improved steadily, the Bence Jones protein excretion fell to a trace, and the serum globulin decreased from 11 2 Gm per cent to 3.4 Gm per cent. After cessation of the ACTH treatment, the bone pains became much worse for about four weeks. There was a gradual spontaneous improvement and the patient became ambulatory Three and one half months after the ACTH was withdrawn, the serum globulin had again risen to 4.7 Gm per cent and Bence Jones proteinuria had reappeared

Pearson and Eliel[141] reported one favorable case Their patient was maintained for five months on cortisone and testosterone propionate treatment Although large numbers of myeloma cells persisted in the bone marrow, the patient felt subjectively well. The serum globulin content dropped markedly, the hemoglobin increased and the renal function improved

Dameshek[45] saw considerable improvement in two cases, with decrease in abnormal plasma proteins and improvement in the marrow and peripheral blood Gardner[64] observed a temporary response with reduction of the plasma protein. Engle and Barr,[58] however, found no improvement in the serum globulin content or the plasma cell proliferation in the bone marrow in three cases of myeloma treated with ACTH Limarzi[107] noted the same negative result in two cases

Effersoe and his associates treated six patients[52,53] and in five cases the bone pains disappeared completely The pathologic serum globulin fell slightly in five patients during the treatment period but rose again after cessation of the ACTH The decrease in the pathologic globulin during treatment was so small that it was nearly within the limits of error of the electrophoretic analysis A decrease in the Bence Jones proteinuria occurred, but there was no significant change in the number of plasma cells in the marrow during or after the treatment The type of the cells and the degree of differentiation remained unchanged In their discussion these authors mention that administration of ACTH and cortisone to hyperimmunized rabbits induces a diminution in the serum antibody concentration and a decrease in the number of plasma cells.[53] In patients with chronic polyarthritis and allergic disorders the increased serum globulin falls during ACTH treatment It seems that myeloma cells are less susceptible to the effects of ACTH and cortisone than are normal plasma cells

We have administered ACTH and cortisone to twenty-three patients in doses comparable to those which have been reported to give favorable results. The results were distinctly unfavorable except for occasional subjective improvement. As an example of the lack of influence of cortisone on most cases of multiple myeloma the following observation may be reported.

This patient, a white riveter 56 years old, was admitted on August 9, 1950 with a history of three years of repeated attacks of fever, usually due to bronchopneumonia These attacks had occurred nearly every month During the year preceding admission he also developed a chronic cough Four months previous to admission, pain developed in the lower anterior ribs and was soon accompanied by dull aching pain in the clavicle, in the spine, and in the right hip The patient also complained of pains in the jaw On admission he appeared extremely ill Bence Jones proteinuria was present The albumin/globulin ratio was 2 6/7.0 The bone marrow smear showed a large number of myeloma cells Radiograms revealed many osteolytic lesions in the skull and mandible Several vertebrae (D 4, D 7, D 9, and L 1) showed compression fractures On admission a bronchopneumonia of the right lower lobe was found. The latter cleared up during antibiotic treatment and bed rest, but the bone pains persisted despite immobilization

On August 25, 1950, this patient was started on cortisone, 100 mg. daily. This compound was administered for about six weeks and was stopped on October 12, 1950 During the cortisone treatment the patient had a transient period of euphoria when the bone pain seemed less severe but shortly thereafter he appeared to go downhill with progressive cachexia The pains in the back and in the ribs soon returned with their original severity The albumin/globulin ratio showed no significant change. He had a persistent low grade fever, continued to produce purulent sputum, and suffered occasionally from bouts of bronchopneumonia On September 4, while he was lying in bed, a complete transverse fracture of his sternum, at the level of the fourth intercostal space, occurred (fig 10)

After cessation of the cortisone treatment, the condition of the patient remained poor. Starting on March 15, 1951, the patient received ten injections of 2-hydroxystilbamidine During this period his anorexia increased and

In only three cases did ACTH or cortisone treatment lead to a significant, though temporary, improvement. The first of these cases has been mentioned before (p. 105) This patient had widespread myeloma of the spine. However, generalization of the myeloma must have been limited, because three bone marrow punctures were negative. In addition, significant improvement had already occurred while on urethane before the *ACTH treatment* was started.

A second patient was admitted in November 1949 with dull pains in the lumbar spine and in the right chest He was not anemic, the blood urea nitrogen was 13 Gm. per cent, the serum albumin 4.3 Gm per cent, the globulin 1.7 Gm per cent. Bence Jones protein was found in the urine The phenolsulphonphthalein excretion amounted to only 12 5 per cent in three hours Roentgen examination revealed the presence of numerous punched out lesions throughout the skeleton In the sternal marrow smear large numbers of myeloma cells were found He was first treated with urethane By February 1950, a total dose of 162 Gm had been administered without the slightest improvement The Bence Jones protein excretion was heavy, the serum albumin was 3 8 Gm per cent, the serum globulin 1 6 Gm per cent

In June 1950 his general condition deteriorated The blood urea nitrogen had risen to 33 mg per cent, the serum creatinine to 6 4 mg per cent At this time ACTH treatment was started with daily doses of 80 mg Under this treatment the bone pains gradually diminished, he became more energetic, his appetite returned, he was able to drive his car, and, after a few months, he resumed his daily work While on ACTH, the blood sugar increased and glycosuria was noted This was easily controlled by small doses of insulin In December 1950 the nonprotein nitrogen of the serum was 76 Gm per cent, the creatinine 4 2 mg per cent, the sedimentation rate of red blood cells only 25 mm per hour On December 29, 1950 he died suddenly, possibly of a pulmonary embolism

In this case ACTH led to subjective well being but there was no objective improvement

Another patient, a 48 year old man, was admitted in June 1950 with severe paroxysms of pain in the back radiating into the legs He required narcotics continuously and was completely bedridden. The skeletal roentgenograms revealed a widespread myeloma, and Bence Jones proteinuria was present The serum albumin was 2 8 Gm per cent, the globulin 3 1 Gm per cent Urethane had been given but had no influence on his pain After ten days of ACTH, 40 mg daily, pain was completely relieved Within a few days he could move around in bed and after a few weeks he was able to walk with the help of an orthopedic corset The serum globulins were not affected, the serum albumin was 3 3 Gm per cent, serum globulin 3 4 Gm per cent The Bence Jones proteinuria similarly did not diminish He developed evidence of renal insufficiency, the blood urea nitrogen was 35 mg per cent, the serum creatinine varied between 4 and 6 mg per cent The bone marrow still contained large numbers of myeloma cells After a few weeks, intense pruritus developed which prevented continuation of the ACTH injections The blood urea nitrogen had increased to 60 mg per cent and the serum creatinine to 11 mg per cent When the ACTH was discontinued, the severe pains recurred Two months later it was again possible to give small amounts of ACTH intermittently and with this therapy he survived for several months However, a sodium poor diet, daily glucose infusions, and frequent blood transfusions were necessary. He

In this patient subjective improvement of pains was also obtained with ACTH The progress of the disease, however, was not halted, the side actions of ACTH were many and intense, and the span of life was not increased.

These patients represent the only favorable observations we have been able to collect from twenty-three patients treated with ACTH and cortisone. Subjective improvement can sometimes be obtained, hyperglobulinemia and Bence Jones proteinuria may be reduced, but nevertheless the favorable influence of cortisone and ACTH upon the course of myeloma is discouragingly small. The main value of these drugs in the treatment of this disease appears to be their ability to produce distinct euphoria with diminished appreciation of pain

Other Chemotherapeutic Methods of Treatment

Rubinstein[153] noted beneficial effects in myeloma from neo-stibosan, including control of bleeding tendency, shrinkage of tumor masses, and improvement of plasma proteins. These results have not been confirmed by others and neo-stibosan has largely been abandoned because it has a nephrotoxic effect in the presence of existing renal damage.

Nitrogen mustard[84] has been reported to have very little beneficial effect in myeloma and our own experience with eight cases confirms this impression Only one patient showed a temporary remission of symptoms which perhaps could be attributed to the drug. Aureomycin, aminopterin, and large doses of testosterone propionate, calcium, and phosphorus have had no effect on symptoms or on the course of the disease

13. SUMMARY

Multiple myeloma is a universally fatal disease, consisting pathologically of a proliferation of immature plasma cells, usually arising in the bone marrow The proliferating cells, designated as myeloma cells, have a basophilic cytoplasm. In the large majority of cases no inclusions are found in the cytoplasm of these cells A fine azurophilic granulation is only rarely present, while somewhat more frequently vacuoles containing protein are seen Fuchsinophilic and acidophilic inclusions, so-called Russell bodies, are mentioned by most authors but are decidedly rare The eccentric nucleus of myeloma cells usually contains one and occasionally two to four nucleoli The chromatin is commonly arranged in clumps resembling a string of sausages Sometimes the chromatin is present in a loosely knit network similar to the nuclear pattern of reticulum cells There is no unanimous opinion regarding the origin of the myeloma cells, but there is increasing adherence to the view that they are derived from the reticulum cells of the bone marrow In most cases the proliferation of myeloma cells is diffuse throughout the bone marrow, so that bone marrow punctures anywhere will yield cells diagnostic of the disease In isolated cases, however, this proliferation is patchy in character and in such patients diagnostic punctures may yield normal bone marrow

Multiple myeloma occurs twice as frequently in men as in women It is limited to no age group, but in the greater majority of cases it occurs in patients over 40 years of age In two thirds of ninety-seven consecutive cases observed at the Mount Sinai Hospital, recognizable symptoms started between the ages of 50 and 70. The youngest patient of this group was 29, the oldest 76 The average period of survival was twenty months, but most of the patients lived less than one and a half

years A few cases survived for several years and one patient died, more than eight years after the first signs of myeloma were recognized.

Anemia is common. Thrombopenia, due to replacement of bone marrow by myeloma cells, occurs frequently. A small number of plasma cells is commonly found in the peripheral blood. Sometimes the peripheral blood is invaded by large numbers of myeloma cells, with a resulting plasma cell leukemia In such cases a leukemia-like infiltration of liver, spleen, lymph nodes, and other visceral organs with myeloma cells is found at autopsy This same visceral infiltration by myeloma cells may also be found at autopsy in patients who have had no signs of plasma cell leukemia during life Because of these findings, many authors designate multiple myeloma as the aleukemic phase of plasma cell leukemia.

Due to the changes in the blood proteins, the sedimentation of the red blood cells is usually very high and rouleau formation is common. A hemorrhagic tendency is frequently seen, not only when thrombopenia exists, but also in patients with a normal platelet count, in whom the hemorrhagic diathesis seems to be related to an increase of abnormal serum globulins Patients with so-called cryoglobulinemia nearly always have a hemorrhagic tendency, and most instances of cryoglobulinemia have been found in patients with myeloma

Bone pain is the most common symptom in multiple myeloma. It is usually localized in the rib cage or the lower back, but also occurs frequently in the hips and shoulders. Pathologic fractures occurred in fifty-nine of our ninety-seven patients, most commonly in the form of compression fractures of one or more vertebrae In 30 per cent of our patients the fractures affected other bones. Although the onset of the disease is usually insidious, it may begin suddenly with a pathologic fracture

In twenty-four of our ninety-seven patients palpable plasmocytomas developed, usually due to perforation of the cortex of an affected bone by proliferating myeloma cells. Palpable tumors are occasionally found in the skull These swellings are nearly always soft or rubbery in consistency. In about 50 per cent of our patients one or more attacks of pneumonia were observed. The well known tendency to development of pneumonia in myeloma may be related partly to increased viscosity of the blood due to hyperglobulinemia and partly to the decrease in the titer of serum antibodies, which is frequent in this disease.

Neurologic signs are common, generally arising from direct compression of the spinal cord or of nerve roots Not infrequently the first sign of the myelomatous disease is compression of the cord Peripheral neuritis, not due to the direct involvement of nerves or nerve roots, is also seen in myeloma

Impairment of renal function is a frequent and serious complication of multiple myeloma, and is seen particularly in those patients who excrete Bence Jones protein in the urine This abnormal protein has a low molecular weight of 35,000 to 40,000 Therefore, it readily passes the glomerular membrane and precipitates as giant casts all through the tubular system. The ensuing tubular blockade must be one of the main causes of the renal insufficiency, but reabsorption, by the tubular epithelium, of large globules of protein, probably Bence Jones protein, may be another reason for tubular damage The uremia caused by a myeloma kidney is hardly ever accompanied by hypertension In our series, twelve patients showed the pathologic picture of the myeloma kidney at autopsy and only one of these had hypertension. The close relation between Bence Jones proteinuria and renal insufficiency is further demonstrated by the fact that all our patients with myeloma kidneys at autopsy had excreted Bence Jones protein during life. Increase of the blood urea nitrogen above 30 mg per cent was found in 55 per cent of all our patients with Bence Jones proteinuria. Such an increase was found in only 24 per cent of our cases with a negative Bence Jones reaction in the urine

Extraskeletal myelomatous involvement is frequent Enlargement of the liver was present in 38 per cent of our patients, enlargement of both liver and spleen in 22 per cent Lymph node enlargement also occurs but is much rarer At autopsy, the enlargement of liver, spleen, and lymph nodes is frequently found to be due to infiltration with myeloma cells

Unexplained fever, possibly due to small patches of pneumonia, is very frequent. Clubbing of the fingers occurs but is rare

The classical roentgenologic picture of a plasmocytoma consists of a punched out osteolytic area without significant degree of osteoblastic reaction Frequently all the bones of the skeleton are riddled by such lesions The x-ray picture of the skull is especially characteristic. Occasionally the roentgen picture of a myelomatous lesion may simulate a giant cell tumor of the bone However, since the latter has a predilection for the long bones, the presence of a lesion resembling a

years. A few cases survived for several years and one patient died, more than eight years after the first signs of myeloma were recognized.

Anemia is common. Thrombopenia, due to replacement of bone marrow by myeloma cells, occurs frequently. A small number of plasma cells is commonly found in the peripheral blood. Sometimes the peripheral blood is invaded by large numbers of myeloma cells, with a resulting plasma cell leukemia In such cases a leukemia-like infiltration of liver, spleen, lymph nodes, and other visceral organs with myeloma cells is found at autopsy. This same visceral infiltration by myeloma cells may also be found at autopsy in patients who have had no signs of plasma cell leukemia during life. Because of these findings, many authors designate multiple myeloma as the aleukemic phase of plasma cell leukemia

Due to the changes in the blood proteins, the sedimentation of the red blood cells is usually very high and rouleau formation is common A hemorrhagic tendency is frequently seen, not only when thrombopenia exists, but also in patients with a normal platelet count, in whom the hemorrhagic diathesis seems to be related to an increase of abnormal serum globulins Patients with so-called cryoglobulinemia nearly always have a hemorrhagic tendency, and most instances of cryoglobulinemia have been found in patients with myeloma.

Bone pain is the most common symptom in multiple myeloma. It is usually localized in the rib cage or the lower back, but also occurs frequently in the hips and shoulders. Pathologic fractures occurred in fifty-nine of our ninety-seven patients, most commonly in the form of compression fractures of one or more vertebrae In 30 per cent of our patients the fractures affected other bones. Although the onset of the disease is usually insidious, it may begin suddenly with a pathologic fracture

In twenty-four of our ninety-seven patients palpable plasmocytomas developed, usually due to perforation of the cortex of an affected bone by proliferating myeloma cells. Palpable tumors are occasionally found in the skull. These swellings are nearly always soft or rubbery in consistency. In about 50 per cent of our patients one or more attacks of pneumonia were observed. The well known tendency to development of pneumonia in myeloma may be related partly to increased viscosity of the blood due to hyperglobulinemia and partly to the decrease in the titer of serum antibodies, which is frequent in this disease.

A completely normal electrophoretic pattern is extremely rare in multiple myeloma

The increased gamma and beta fractions of myeloma sera are not identical with the gamma and beta fractions found in normal sera The gamma and beta peaks seen in the electrophoretic curves derived from myeloma sera are extremely sharp, much sharper than the peaks found in the sera of patients with hyperglobulinemia due to other diseases, such as liver cirrhosis, kala azar, chronic hypersensitivity, acute lupus erythematosus, subacute bacterial endocarditis, etc. Chemical and immunologic differences between the beta and gamma globulin of myeloma sera and of normal sera also exist

The changes of the electrophoretic patterns in myeloma sera are not due, to any significant degree, to the presence of Bence Jones protein The presence of Bence Jones protein in serum and other body fluids can best be demonstrated by immunologic methods No more than 0 2 Gm per cent of this protein has been found in myeloma sera with this method This quantity is so small that it can only be determined by immunologic and not by chemical or electrophoretic methods This tiny amount is insufficient to explain the large and abnormal amounts of beta or gamma globulin in the myeloma sera

At the Mount Sinai Hospital the sera of forty-four patients with multiple myeloma were examined electrophoretically Four of these cases showed an increase of the alpha fraction, six of the beta fraction, and twenty-one of the gamma fraction In thirteen cases only minor anomalies of the electrophoretic pattern could be elicited, and in these cases, the Howe fractionation showed completely normal figures. In the cases with marked hyperglobulinemia, Bence Jones proteinuria occurred much less frequently than in the patients with minor anomalies of the electrophoretic patterns Only seven of the thirty-one cases with electrophoretically proved hyperglobulinemia excreted Bence Jones protein in the urine However, ten of our thirteen cases with minor electrophoretic anomalies had Bence Jones protein in the urine There is some reason to believe that both Bence Jones protein and the abnormal serum globulins in multiple myeloma are synthesized by the myeloma cells

It can be shown by ultracentrifugation that the different globulin fractions which can be separated by electrophoresis are not homogeneous. Both beta and gamma globulins of myeloma patients have

giant cell tumor in a flat bone, especially in the pelvis, is good reason to suspect the presence of a plasmocytoma.

In multiple myeloma three remarkable changes in protein metabolism, Bence Jones proteinuria, hyperglobulinemia, and paramyloidosis, are frequently observed

The presence of Bence Jones protein should only be considered as certain when a substance is found which both precipitates at 45 C. and dissolves at 95 C When it occurs, it is almost pathognomonic for the diagnosis of multiple myeloma. The alleged occurrence of Bence Jones proteinuria in rare cases of lymphatic leukemia can usually be explained by a confusion between the latter disease and plasma cell leukemia The appearance of myeloma cells in the peripheral blood often differs from that of myeloma cells in the bone marrow, and these can easily be mistaken for young lymphocytes Bence Jones protein occurs in about 50 per cent of the cases of multiple myeloma This abnormal protein can be crystallized in the test tube; it has also been noted to crystallize within the body tissues.

In about 60 per cent of the cases of myeloma the globulin content of the serum is increased, usually leading to hyperproteinemia when the albumin of the serum is not significantly decreased. However, the hyperglobulinemia in multiple myeloma is often accompanied by a marked decrease of the serum albumin, so that there are many cases of multiple myeloma with hyperglobulinemia but without hyperproteinemia.

The presence of hyperglobulinemia can be detected by the sodium sulfate precipitation as first devised by Howe or by one of the modifications of this method. There may be an increase of the euglobulin fraction alone or of the pseudoglobulin fraction alone or both fractions may be increased at the same time Electrophoretic separation of the different globulin fractions of the serum shows that the hyperglobulinemia in multiple myeloma is most frequently due to an increase of the gamma fraction; an increase of the beta fraction is much less common, while an increase of the alpha fraction occurs only rarely Often the larger part of the globulins consists of a fraction which, during electrophoresis, migrates more rapidly than the gamma but less rapidly than the beta globulin, the so-called M protein. There remains a considerable group of cases where only minor anomalies of the globulin fractions can be discovered by electrophoretic separation In such cases the results of the Howe fractionation are always normal.

A completely normal electrophoretic pattern is extremely rare in multiple myeloma.

The increased gamma and beta fractions of myeloma sera are not identical with the gamma and beta fractions found in normal sera. The gamma and beta peaks seen in the electrophoretic curves derived from myeloma sera are extremely sharp, much sharper than the peaks found in the sera of patients with hyperglobulinemia due to other diseases, such as liver cirrhosis, kala azar, chronic hypersensitivity, acute lupus erythematosus, subacute bacterial endocarditis, etc. Chemical and immunologic differences between the beta and gamma globulin of myeloma sera and of normal sera also exist.

The changes of the electrophoretic patterns in myeloma sera are not due, to any significant degree, to the presence of Bence Jones protein. The presence of Bence Jones protein in serum and other body fluids can best be demonstrated by immunologic methods. No more than 0.2 Gm. per cent of this protein has been found in myeloma sera with this method. This quantity is so small that it can only be determined by immunologic and not by chemical or electrophoretic methods. This tiny amount is insufficient to explain the large and abnormal amounts of beta or gamma globulin in the myeloma sera.

At the Mount Sinai Hospital the sera of forty-four patients with multiple myeloma were examined electrophoretically. Four of these cases showed an increase of the alpha fraction, six of the beta fraction, and twenty-one of the gamma fraction. In thirteen cases only minor anomalies of the electrophoretic pattern could be elicited, and in these cases, the Howe fractionation showed completely normal figures. In the cases with marked hyperglobulinemia, Bence Jones proteinuria occurred much less frequently than in the patients with minor anomalies of the electrophoretic patterns. Only seven of the thirty-one cases with electrophoretically proved hyperglobulinemia excreted Bence Jones protein in the urine. However, ten of our thirteen cases with minor electrophoretic anomalies had Bence Jones protein in the urine. There is some reason to believe that both Bence Jones protein and the abnormal serum globulins in multiple myeloma are synthesized by the myeloma cells.

It can be shown by ultracentrifugation that the different globulin fractions which can be separated by electrophoresis are not homogeneous. Both beta and gamma globulins of myeloma patients have

the same sedimentation constant on ultracentrifugation (S7) and therefore have similar molecular weights.

In a disease described by Waldenström the increased serum globulins have a very high sedimentation constant of S 19-20. This disease, which he has designated as macroglobulinemia, is possibly different from multiple myeloma, since macroglobulins are only rarely found in the sera of myeloma patients

The third anomaly of protein metabolism in multiple myeloma consists of paramyloidosis In this condition amyloid is deposited in atypical locations, especially in mesodermal tissues, such as the [illegible] tongue, and in the [illegible] asional case of myeloma with paramyloidosis, [illegible] in the liver, kidneys, and spleen This is in striking contrast to the secondary amyloidosis developing after chronic suppuration, in which the amyloid is deposited in liver, kidneys, spleen, adrenals, and also in the blood vessel walls. The deposition of paramyloid may give rise to remarkable clinical symptoms and signs. Macroglossia in a myeloma patient is nearly always a sign of deposition of paramyloid Some patients with myeloma develop unexplained heart failure and at autopsy this is shown to be caused by amyloidosis of the myocardium In one of our myeloma patients severe intestinal bleeding was due to amyloidosis of the intestinal wall In another patient large hard masses were deposited in the subcutaneous layers of the skin over the lower chest and upper abdomen, paramyloid "en cuirasse". Congo red tests are of little value in the diagnosis of paramyloid because the liver is usually spared A gingival biopsy occasionally shows the deposition of paramyloid in the blood vessels

The calcium content of the serum in multiple myeloma is often increased, probably as a result of rapid demineralization of the skeleton In 38 per cent of our cases, the serum calcium exceeded 12 mg. per cent The highest value recorded was 17.5 mg. per cent High values for the serum calcium often indicate advanced disease and a poor prognosis The inorganic serum phosphorus is normal except in the presence of uremia, when it is generally elevated. The alkaline phosphatase of the serum is usually normal. This sign has differential diagnostic value because in many other instances of demineralizing diseases of the skeleton, the alkaline phosphatase is increased. In 83 per cent of our cases the alkaline phosphatase of the

serum was completely normal. The other 17 per cent exhibited elevations of the serum phosphatase at one time or another, in general in the presence of large fractures. Liver damage, especially in the course of urethane treatment, is another reason for increase of the alkaline phosphatase of the serum When, in the absence of pathologic fractures or liver disease, the serum phosphatase remains elevated, the diagnosis of multiple myeloma should be questioned.

Metastatic calcification occurs occasionally in multiple myeloma. Four of our forty autopsied cases had renal stones, and one had microscopic calcifications in the lungs. The uric acid content of the serum is often elevated in multiple myeloma This must be due to increased destruction of the cytoplasm and nuclei of proliferating myeloma cells, just as is the case in myeloid and lymphatic leukemia In 50 per cent of our cases the uric acid content of the serum exceeded 7 mg. per cent.

Solitary plasmocytomas occur, but are decidedly rare In most cases of so-called solitary plasmocytoma, it is possible to find evidence that generalization has already taken place Bone marrow punctures are of the greatest importance in uncovering such generalization Nevertheless, there are rare observations of plasmocytomas which have remained solitary for many years In addition there are patients who, in the course of years, develop multiple tumors consisting of proliferating myeloma cells in different parts of the skeleton without signs of generalized bone marrow involvement In such cases typical generalized myelomatosis can still develop after several years It seems justified to consider these cases of multiple plasmocytomas without generalized proliferation of myeloma cells as representing the initial stage of multiple myeloma.

Extramedullary plasmocytomas also occur without accompanying osseous involvement They occur especially in the mucous membranes of the nose, paranasal sinuses, pharynx, and larynx, and occasionally also in other organs Sometimes these tumors remain localized, but in many cases the complete picture of multiple myeloma ultimately develops

The diagnosis of multiple myeloma is often easy However, sometimes differentiation from postmenopausal osteoporosis, osteomalacia, hyperparathyroidism, and skeletal metastases may offer considerable difficulties Multiple myeloma may also appear as unexplained anemia, lymphatic leukemia, giant cell tumors of bone, chronic

glomerulonephritis, and fever of unknown origin. When bone pain is absent, the diagnosis is especially difficult.

The treatment of multiple myeloma is still highly unsatisfactory. Radiotherapy affords palliative relief especially when a plasmocytoma exerts pressure on adjacent structures. Stilbamidine and 2-hydroxystilbamidine, urethane, cortisone, and ACTH may all be followed by periods of apparent well being The course of the disease may be slowed, but ultimately the span of life is not significantly prolonged. It is somewhat encouraging that urethane and sometimes cortisone and ACTH, in contrast to stilbamidine, may reduce the hyperglobulinemia and Bence Jones proteinuria. It seems, therefore, that these agents actually have an effect upon the disease, although they have no permanent curative action Radioactive phosphorus, *nitrogen mustard, testosterone propionate, aminopterin, aureomycin,* and neostibosan have all been tested but have been found to be of little value.

BIBLIOGRAPHY

[1] Adams, W S, Alling, E L, and Lawrence, J S Multiple myeloma Its clinical and laboratory diagnosis with emphasis on electrophoretic abnormalities Am J Med. *6* 141, 1949

[2] Adams, A R D and Yorke, W A case of Indian kala-azar treated with 4 4′ diamidino-stilbene Ann. Trop Med *33* 323, 1939

[3] Adams, W and Dowse, T S Mollities ossium Tr Path Soc London *23* 186, 1872

[4] Albers, H Multiple Myeloma und Viscositat Ztschr klin Med *132* 807, 1937

[5] Allen, A C The Kidney, New York, Grune & Stratton, 1951

[6] Alwall, N Urethane and stilbamidine in multiple myeloma Report on two cases Lancet *2* 388, 1947

[7] Anders, J M. and Boston, L N Bence-Jones Albumosuria with report of three cases Lancet *1* 93, 1903

[8] Apitz, K Die Paraproteinosen (über die Storung des Eiweiss-Stoffwechsels beim Plasmocytom) Virch Arch path Anat *306* 631, 1940

[9] Arai, H and Snapper, I The influence of stilbamidine upon kidney function, liver function and peripheral blood in multiple myeloma N Y State J Med *47* 1867, 1947

[10] Arinkin, M I Die intravitale Untersuchungsmethodik des Knochenmarks Folia Haemat *38* 233, 1929

[11] Armstrong, J B A study of renal function in patients with multiple myeloma Am J. M Sc *219* 488, 1950

[12] Askanazy, S Ueber die diagnostiche Bedeutung der Ausscheidung des Bence-Jonesschen Körpers durch den Harn Deutsches Arch f klin Med *68* 34, 1900

[13] Atkinson, F R B Multiple Myelomata M Press *195* 327, 1937

[14] Aufses, A A Solitary myeloma of rib J Mt Sinai Hosp *15* 150, 1948

[15] Barr, D, Reader, G C, and Wheeler, D H Cryoglobulinemia, report of two cases Discussion of clinical manifestations, incidence, and significance Ann Int Med *32* 6, 1950

[16] Batts, M Multiple myeloma, review of 40 cases Arch Surg *39* 807, 1939

[17] Bayne-Jones, S and Wilson, D W Immunological reactions of Bence-Jones proteins II Differences between Bence-Jones proteins from various sources Bull Johns Hopkins Hosp *33* 119, 1922

[18] Bayrd, E D. The bone marrow on sternal aspiration in multiple myeloma Blood *3* 987, 1948

[19] Bayrd, E D and Heck, F J Multiple myeloma, a review of 83 proved cases J A M A *133* 147, 1947

[20] Bell, E T Renal lesions associated with multiple myeloma Am J Path *9* 393, 1933

glomerulonephritis, and fever of unknown origin. When bone pain is absent, the diagnosis is especially difficult.

The treatment of multiple myeloma is still highly unsatisfactory Radiotherapy affords palliative relief especially when a plasmocytoma exerts pressure on adjacent structures Stilbamidine and 2-hydroxystilbamidine, urethane, cortisone, and ACTH may all be followed by periods of apparent well being. The course of the disease may be slowed, but ultimately the span of life is not significantly prolonged It is somewhat encouraging that urethane and sometimes cortisone and ACTH, in contrast to stilbamidine, may reduce the hyperglobulinemia and Bence Jones proteinuria. It seems, therefore, that these agents actually have an effect upon the disease, although they have no permanent curative action Radioactive phosphorus, *nitrogen mustard*, *testosterone propionate*, *aminopterin*, *aureomycin*, and neostibosan have all been tested but have been found to be of little value.

[46] DAVISON, C. AND BALSER, B. A: Myeloma and its neural complications. Arch. Surg *35* 193, 1937.

[47] VON DECASTELLO, A. Beitrage zur Kenntnis der Bence-Jonesschen Albuminurie Ztschr klin Med *67* 319, 1908–9.

[48] DENT, C E AND ROSE, G A · The Bence Jones protein of multiple myelomatosis, its methionine content and its possible significance in relation to the aetiology of the disease Biochem J. *44* 610, 1949

[49] DENT, C E AND ROSE, G. A.. A physical and chemical study of Bence Jones protein with especial reference to its methionine content and the possible significance of this Biochem J. *43* 14, 1948

[50] DOWNEY, H Handbook of Haematology. New York, Hoeber, 1938

[51] DUVOIR, M, POLLET, L, LAYANI, F, DECHAUME, M, AND GAULTIER, M.· Myélomes multiples avec tumeurs cutanées, intérêt nosographique Bull. et mém. Soc. Méd Hôp Paris *54* 687, 1938

[52] EFFERSOE, P Effect of ACTH and Cortisone upon Serum Proteins, Scandinav. J. Clin & Lab Investigation *2* 265, 1950

[53] EFFERSOE, P, GORMSEN, H, HARBOE, N, NIELSEN, S E, AND VIDEBAEK A On the effect of corticotropin ACTH on myelomatosis with special reference to the bone marrow and the serum proteins Acta med Scandinav *143* 63, 1952

[54] EHRICH, W Die Nierenerkrankung bei Bence-Jonesscher Proteinurie Ztschr klin Med *121* 396, 1932

[54a] EISEN, H N Primary systemic amyloidosis, Am. J Med *1* 144, 1946

[55] ELLINGER, A Das Vorkommen des Bence-Jonesschen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung Deutsche Arch klin Med *62* 255, 1899

[56] ELSON, W O The antibacterial and fungostatic properties of propamidine J. Infect Dis *76* 193, 1945

[57] ENGEL, L L Discussion remarks, in Proceedings of the Second Clinical ACTH Conference, vol 2, 1951, p 217.

[58] ENGLE, R L AND BARR, D P Multiple myeloma treated with ACTH Proceedings of the Second Clinical ACTH Conference, vol 2, 1951, p 209

[59] ERF, A AND HERBERT, P A Comparative cytology of Wright's stained smears and histologic sections in multiple myeloma Am J Clin Path *16* 1, 1946

[60] FAGREAUS, A Antibody production in relation to the development of plasma cells Acta med Scandinav Supp *130* 204, 1948

[61] FAHRAEUS, R The suspension stability of the blood Acta med Scandinav *55* 1, 1921

[62] FULTON, J. D The prophylactic action of various aromatic diamidines in trypanosomiases of Mice Ann Trop Med *38* 78, 1944

[63] FURTH, J Transmission of myeloid leukemia in mice J Exper Med *61* 423, 1935

[64] GARDNER, F Discussion remarks, Blood Club proceedings ACTH in leukemia Blood *5* 791, 1950

[65] GARLAND, L H AND KENNEDY, B. R Roentgen treatment of multiple myeloma Radiology *50* 297, 1948

[66] GESCHICKTER, C F AND COPELAND, M M Multiple myeloma Arch. Surg *16* 807, 1928.

[67] GLAUS, A Uber multiples Myelomazytom mit Eigenartigen zum Teil Kristallähnlichen Zelleinlagerungen mit Elastolyse und ausgedehnter Amyloidose und Verkalkung Virchow's Arch. Path Anat. *223* 301, 1917

[68] GLUZINSKI, A AND REICHENSTEIN, M Myeloma und Leucemia lymphatica plasmacellularis Wien klin Wchnschr *19*.336, 1906.

[21] BENCE JONES, H On a new substance occurring in the urine of a patient with "mollities ossium" Phil Tr Royal Soc London, 1848, p 55

[22] BERHEISER, E J Multiple myeloma of children Arch Surg 8 853, 1928.

[23] BESSIE, M Cytologie Sanguine Normale et Pathologique Paris, Masson et Cie., 1948

[24] BETHEL, F H Discussion remarks, in, Proceedings of the Second Clinical ACTH Conference, vol 2, 1951, p 216

[25] BICHEL, J Diamidines in myelomatosis. Acta radiol 37 65, 1952.

[26] BICHEL, J, BING, J, AND HARBOE, N Another case of hyperglobulinemia and affection of the central nervous system Acta med Scandinav 138 1, 1950.

[27] BICHEL, J, EFFERSOE, P, GORMSEN, H, AND HARBOE, N Leukemic myelomatosis (plasma cell leukemia) Acta radiol 37 196, 1952

[28] BICHEL, J AND KIRKETERP, P Notes on myeloma Acta radiol 19 487, 1938

[29] BING, J, FAGRAEUS, A, AND THORELL, B Studies on nucleic acid metabolism in plasma cells Acta physiol Scandinav 10 282, 1945

[30] BING, J AND PLUM, P Serum proteins in leucopenia Acta med Scandinav. 92.415, 1937

[31] BJORNEBOE, M AND GORMSEN, H Untersuchungen uber das Vorkommen von Plasmazellen bei experimenteller Hyperglobulinämie bei Kaninchen Klin Wchnschr 20 314, 1941

[31a] BLACKMAN, C, BARKER, W, BUELL, M, AND DAVIS, B On the pathogenesis of renal failure associated with multiple myeloma Electrophoretic and chemical analysis of protein in urine and blood serum J Clin Investigation 23 163, 1944.

[32] CAPPELL, D AND MATHERS, R Plasmacytoma of the petrous temporal bone and base of skull J. Laryng & Otol 50 340, 1935

[33] CARTER, J R Plasma cell hyperplasia and hyperglobulinemia in trichinosis Am J Path 25 309, 1949

[34] CHOJNACKI, P Ein Beitrag zur Kenntnis der plasmozytaren Granulome (Plasmomata Conjunctivae) Klin Monatsbl f Augenh 95 470, 1935.

[35] CHRISTIAN, H A. Multiple myeloma, a histological comparison of six cases J Exper Med 9 325, 1907

[36] CHRISTOPHERSON, W M AND MILLER, A J A re-evaluation of solitary plasma cell myeloma of the bone Cancer 3 240, 1950

[36] CHURG, J AND GORDON, A Multiple myeloma with unusual visceral involvement Arch Path 34 546, 1942

[37] CHURG, J AND GORDON, A J Multiple myeloma, lesions of the extra-osseous hematopoietic system Am. J Clin Path 20 934, 1950

[38] COLLARD, P. J AND HARGREAVES, W H Neuropathy after stilbamidine treatment Lancet 2 686, 1947

[39] COLLIER, F C, REICH, A, AND KING, J W The value of precipitin tests for Bence-Jones protein in early diagnosis N England J Med 247 60, 1952

[40] CORCORAN, A C AND PAGE, I H Renal damage from ferroheme pigments, myoglobin, hemoglobin, hematin Texas Rep Biol & Med 3 528, 1945

[41] COURVILLE, C G Notes on the pathology of cranial tumors Tumors originating in the marrow of the diploe Bull Los Angeles Neuro Soc 13 19, 1948

[42] DAHLIN, D C Amyloidosis Proc Staff Meet Mayo Clin 24 637, 1949

[43] DALGAARD, E B AND DALGAARD, J B Solitary plasmocytoma with terminal dissemination Acta radiol 37 231, 1952.

[44] DALRYMPLE, J On the microscopic character of mollities ossium. Dublin Quart J. M Sc 2 85, 1846

[45] DAMESHEK, W Blood Club proceedings ACTH in leukemia Blood 5 791, 1950.

[89] Kabelitz, von H.: Plasmazellen und Eiweissstoffwechsel Acta. haemat. *5* 232, 1951.

[90] Kahler, O · Zur Symptomatologie des multiplen Myeloms, Beobachtung von Albumosurie Prag Med Wchnschr. *14* 33 45, 1889

[91] Kesterson, J and McSwain, B.. Myeloma of bone. J. Bone & Joint Surg *34A*.224, 1952.

[92] Kin, S S . Beitrag zur Kenntnis der Kahlerschen Krankheit mit Mycosis Fungoides, Besonders über die Genese der Geschwulstzellen Arch. f Jap Chir *16* 79, 1939

[93] Klemperer, P.: Über das Lymphoblastische und das Plasmacellulare Myeloma. Beitr. path Anat *67*.492, 1920

[94] Kopac, M J · The action of diamidines and related compounds on nucleoproteins Cancer Res *7* 44, 1947.

[94a] Krainin, P , D'Angio, C J , and Smelin, A Multiple myeloma with new bone formation Arch Int Med *84* 976, 1949

[95] Kreuzer, H Plasmacellulares Myelom mit multipler teilweise hemorrhagischer Herd Myelose der Medulla Spinalis Deutsche Ztschr Nervenh. *90*.224, 1926

[96] [illegible]

[97] Kunkel, H G and Hoagland, C L. Mechanism and significance of the thymol turbidity test for liver disease. J Clin. Investigation *26* 1060, 1947

[98] Kunkel, H. G , Slater, R J , and Good, R A Relation between certain myeloma proteins and normal gamma globulin Proc Soc Exper Biol & Med *76* 190, 1951.

[99] Kurnick, N. B , Klein, G , and Klein, E Effect of sulbamidine on ascites tumor of mice Experientia *4* 152, 1950.

[100] Kurnick, N B and Yohalem, S B Peripheral neuritis complicating multiple myeloma Arch Neurol & Psychiat. *59* 378, 1948.

[101] Lane, S L Plasmocytoma of the mandible Oral Surg *5* 434, 1952

[102] Lawrence, J H and Rosenthal, R L · Multiple myeloma associated with polycythemia, report of 4 cases Am J Med Sc *218* 149, 1949

[102a] Léger, L , Ducroquet, R , and Léger H Maladies du Squelette Paris, Masson, 1949, p 233

[103] Levin, B , Oberholzer, V G , and Whitehead, T P Serum protein fractions A comparison of precipitation methods with electrophoresis J. Clin Path *3* 260, 1950

[104] Lewis, L A , Bortz, D W , and Battle, J D , Jr Electrophoretic and ultracentrifugal analysis of serum proteins in multiple myeloma. Cleveland Clin Quart *18* 119, 1951

[105] Lichtenstein, L and Jaffe, H L Multiple myeloma a survey based on 35 cases, eighteen of which came to autopsy. Arch Path *44* 207, 1947

[106] Lindeboom, G A and Mulder, H J Multiples Myelom mit leukämischen und degenerativen Rückenmarksänderungen Acta med Scandinav *8* 363, 1941

[107] Limarzi, L R.· Diagnostic and therapeutic aspects of multiple myeloma M Clin North America *35* 189, 1951

[108] Lisco, H Russell bodies occurring in the Lymph Follicles of the Intestinal Tract of Pigs Anat. Rec *82* 59, 1942

[109] Loge, J P and Rundles, R W Urethane (ethylcarbamate) therapy in multiple myeloma Blood *4* 201, 1949.

[68a] GOLDMAN, R., ADAMS, W. S., AND LUCHSINGER, E.: Renal function in multiple myeloma. J. Lab. & Clin. Med. 40:519, 1952.

[68b] GOLTZ, R. W.: Systematized amyloidosis. Medicine 31:381, 1952.

[69] GUNN, F. D. AND MAHLE, A. E.: Megakaryoblastic myeloma with crystalline protein in the renal tubules, report of a case. Arch. Path. 26:377, 1938.

[70] GUTMAN, A. B.: The plasma proteins in disease, in, Anson, M. L. and Edsall, J. T. (eds.): Advances in Protein Chemistry, New York, Academic Press, 1948, vol. 4, pp. 156–250.

[71] GUTMAN, A. B., MOORE, D. H., GUTMAN, E. B., MCCLELLAND, V., AND KABAT, E. A.: Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. J. Clin. Investigation 20:765, 1941.

[72] GUTMAN, A. B., TYSON, T. L., AND GUTMAN, E. B.: Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma, and neoplastic diseases of the bones. Arch. Int. Med. 57:379, 1936.

[73] HAEDICKE, T. A. AND GREENSPAN, E. M.: Massive stilbamidine therapy of multiple myeloma. Am. J. Clin. Path. 19:634, 1949.

[74] HAYNES, R. D., POWELL, W. N., AND BAILEY, H. A.: Multiple myeloma, its treatment with urethane and ACTH. South. M. J. 44:467, 1951.

[75] HALL, B. E. AND WATKINS, C. H.: Radiophosphorus in the treatment of blood dyscrasias. M. Clin. North America 31:810, 1947.

[75a] HASS, G. M., HUNTINGTON, R., and KRUMDIECK, N.: Amyloid: the properties of amyloid deposits occurring in several species under diverse conditions. Arch. Path. 35:226, 1943.

[76] HEKTOEN, L. AND WELKER, W. H.: Immunological differences of crystalline Bence Jones proteins. Biochem. J. 34:487, 1940.

[77] HEILMEYER, L.: Therapie mit cytostatischen Stoffen. Acta haemat. 2:25, 1949.

[78] HEISER, S. AND SCHWARTZMAN, J.: Variations in the roentgen appearance of the skeletal system in myeloma. Radiology 58:178, 1952.

[79] HELLWIG, C. A.: Extramedullary plasma cell tumors as observed in various locations. Arch. Path. 36:95, 1943.

[80] HILL, R. M., MULLIGAN, R. M., AND DUNLOP, S. G.: Plasma cell myeloma associated with high concentration of plasma lipoprotein. Am. J. Path. 24:689, 1948.

[81] HOWE, P. E.: The use of sodium sulphate as the globulin precipitant in the determination of proteins in blood. J. Biol. Chem. 49:93, 1921.

[82] JACKSON, H., JR., PARKER, F., JR., AND BETHEA, J. M.: Studies of diseases of the lymphoid and myeloid tissues. II. Plasmocytoma and their relation to multiple myelomata. Am. J. Med. Sc. 181:169, 1931.

[83] JACOBSON, B. M. AND WILNER, L. W.: The detection of urinary Bence-Jones protein. Am. J. Clin. Path. 14:138, 1944.

[84] JACOBSON, L. O., SPURR, C. L., BARRON, E. S. G., SMITH, T., LUSHBAUGH, C., AND DICK, G. F.: Nitrogen mustard therapy: studies on the effect of methyl-bis (beta-chloroethyl) amino hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system. J. A. M. A. 132:263, 1947.

[85] JACOBSON, V. C.: A case of multiple myelomata with chronic nephritis showing Bence-Jones protein in the urine and blood serum. J. Urol. 1:167, 1917.

[86] JACOX, H. W. AND KAHN, E. A.: Multiple myeloma with spinal cord involvement. Am. J. Roentgenol. 30:201, 1933.

[87] JAEGER, E.: Das Extramedullare Plasmocytom. Ztschr. f. Krebsforsch. 52:349, 1942.

[88] JANSSEN, L. W.: Electrophoretic studies on serum proteins. Verhand. Kon. Nederl. Akad. Wetenschappen, sect. II 47.

[89] KABELITZ, VON H.: Plasmazellen und Eiweissstoffwechsel Acta haemat. 5.232, 1951.

[90] KAHLER, O. Zur Symptomatologie des multiplen Myeloms, Beobachtung von Albumosurie Prag Med. Wchnschr *14* 33 45, 1889

[91] KESTERSON, J AND MCSWAIN, B. Myeloma of bone J. Bone & Joint Surg. *34A* 224, 1952

[92] KIN, S S. Beitrag zur Kenntnis der Kahlerschen Krankheit mit Mycosis Fungoides, Besonders über die Genese der Geschwulstzellen Arch. f Jap Chir *16* 79, 1939

[93] KLEMPERER, P.· Über das Lymphoblastische und das Plasmacellulare Myeloma Beitr. path Anat *67* 492, 1920

[94] KOPAC, M J The action of diamidines and related compounds on nucleoproteins Cancer Res *7* 44, 1947

[94a] KRAININ, P, D'ANGIO, C J, AND SMELIN, A Multiple myeloma with new bone formation Arch Int Med *81* 976, 1949

[95] KREUZER, H Plasmacellulares Myelom mit multipler teilweise hemorrhagischer Herd Myelose der Medulla Spinalis Deutsche Ztschr Nervenh *90* 224, 1926

[96] [illegible]

[97] KUNKEL, H G AND HOAGLAND, C L Mechanism and significance of the thymol turbidity test for liver disease J Clin Investigation *26* 1060, 1947.

[98] KUNKEL, H G, SLATER, R J, AND GOOD, R A. Relation between certain myeloma proteins and normal gamma globulin Proc. Soc Exper Biol & Med *76* 190, 1951.

[99] KURNICK, N B, KLEIN, G, AND KLEIN, E · Effect of sulbamidine on ascites tumor of mice Experientia *4* 152, 1950

[100] KURNICK, N. B AND YOHALEM, S B Peripheral neuritis complicating multiple myeloma Arch. Neurol & Psychiat *59* 378, 1948

[101] LANE, S L Plasmocytoma of the mandible Oral Surg *5* 434, 1952

[102] LAWRENCE, J H AND ROSENTHAL, R. L Multiple myeloma associated with polycythemia, report of 4 cases Am. J Med Sc *218*.149, 1949.

[102a] LÉGER, L, DUCROQUET, R, AND LÉGER H Maladies du Squelette Paris, Masson, 1949, p 233

[103] LEVIN, B, OBERHOLZER, V G, AND WHITEHEAD, T P Serum protein fractions A comparison of precipitation methods with electrophoresis J Clin Path *3* 260, 1950

[104] LEWIS, L A, BORTZ, D W, AND BATTLE, J D, JR Electrophoretic and ultracentrifugal analysis of serum proteins in multiple myeloma. Cleveland Clin Quart *18* 119, 1951

[105] LICHTENSTEIN, L AND JAFFE, H. L Multiple myeloma a survey based on 35 cases, eighteen of which came to autopsy Arch Path *44* 207, 1947.

[106] LINDEBOOM, G A. AND MULDER, H J Multiples Myelom mit leukämischen und degenerativen Rückenmarksänderungen Acta med. Scandinav *8* 363, 1941.

[107] LIMARZI, L R Diagnostic and therapeutic aspects of multiple myeloma *M Clin North America 35 189, 1951*

[108] LISCO, H. Russell bodies occurring in the Lymph Follicles of the Intestinal Tract of Pigs Anat. Rec *82* 59, 1942

[109] LOGE, J P AND RUNDLES, R W Urethane (ethylcarbamate) therapy in multiple myeloma Blood *4* 201, 1949

[68a] Goldman, R., Adams, W. S, and Luchsinger, E. Renal function in multiple myeloma. J Lab & Clin. Med *40*.519, 1952
[68b] Goltz, R W.· Systematized amyloidosis Medicine *37*.381, 1952
[69] Gunn, F D and Mahle, A E.· Megakaryoblastic myeloma with crystalline protein in the renal tubules, report of a case. Arch. Path. *26* 377, 1938
[70] Gutman, A B. The plasma proteins in disease, in, Anson, M. L and Edsall, J. T. (eds) Advances in Protein Chemistry, New York, Academic Press, 1948, vol. 4, pp 156–250
[71] Gutman, A. B., Moore, D. H, Gutman, E. B, McClelland, V., and Kabat, E A : *Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma.* J Clin. Investigation *20* 765, 1941.
[72] Gutman, A B., Tyson, T L., and Gutman, E. B. Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma, and neoplastic diseases of the bones Arch Int Med *57*.379, 1936
[73] Haedicke, T A and Greenspan, E. M.· Massive stilbamidine therapy of multiple myeloma Am J. Clin Path. *19* 634, 1949.
[74] Haines, R D, Powell, W N., and Bailey, H. A. Multiple myeloma, its treatment with urethane and ACTH South M J. *44* 467, 1951
[75] Hall, B E and Watkins, C H. Radiophosphorus in the treatment of blood dyscrasias M. Clin. North America *31*.810, 1947
[75a] Hass, G M, Huntington, R, and Krumdieck, N Amyloid the properties of amyloid deposits occurring in several species under diverse conditions Arch Path *35* 226, 1943
[76] Hektoen, L and Welker, W H.. Immunological differences of crystalline Bence Jones proteins Biochem J. *34* 487, 1940
[77] Heilmeyer, L Therapie mit cytostatischen Stoffen Acta haemat *2* 25, 1949.
[78] Heiser, S and Schwartzman, J · Variations in the roentgen appearance of the skeletal system in myeloma Radiology *58* 178, 1952
[79] Hellwig, C. A Extramedullary plasma cell tumors as observed in various locations Arch. Path *36* 95, 1943.
[80] [illegible]
[81] [illegible] 1931
[82] [illegible] es of diseases of the [illegible] relation to multiple [illegible]
[83] [illegible] inary Bence-Jones protein Am J. Clin Path. *14*.138, 1944
[84] Jacobson, L O, Spurr, C. L, Barron, E S G, Smith, T., Luchbaugh, C, and Diek, G F Nitrogen mustard therapy studies on the effect of methyl-bis (beta-chlorethyl) amino hydrochloride on neoplastic diseases and allied dis- [illegible] J. A. M. A. [illegible] 1947
[85] Ja [illegible]
[86] Ja [illegible] Am J. Roentgenol [illegible]
[87] Jaeger, E.· Das Extramedullare Plasmocytom Ztschr. f. Krebsforsch *52 349, 1942*
[88] Janssen, L W.: Electrophoretic studies on serum proteins. Verhand Kon Nederl. Akad Wetenschappen, sect. II *47*.

Scandinavian Congress of Internal Medicine, Copenhagen, June 27, 1948 Acta med Scandinav Supp *230* 86, 1950

[135] OLHAGEN, B Modern analyses of blood protein Nord med. *34* 992, 1947

[136] OLHAGEN, B On the correlation between the electrophoretic pattern and certain simple globulin reactions of human serum (the formol gel, Takata and Weltmann tests) Acta med Scandinav Supp. *196* 478, 1947

[136a] OLHAGEN, B , THORELL, B , AND WISSING, P.. The endocellular nucleic acid distribution and plasmaprotein formation in myelomatosis Scand J Clin Lab Investigation *1* 49, 1949

[137] OLIVER, J : New directions in renal morphology, a method, its results, and its future Harvey Lectures *40* 102, 1944–45

[137a] PAIGE, B H A case of myeloma with unusual amyloid deposition Am J Path *7* 691, 1931

[138] PARISER, S , ZUCKER, R A , AND MEYER, L. M Hematologic changes associated with the immune responses in man Acta med Scandinav. *144* 201, 1952

[138a] PATTERSON, E , HADDOW, A , THOMAS, J. A , AND WATKINSON, J M Leukaemia treated with urethane Lancet *250* 677, 1946

[139] PA

[140] PE

the cytochemistry of plasma cells and reticulum cells J Clin Path *2* 81, 1949

[141] PEARSON, O H AND ELIEL, L P . Use of ACTH and cortisone in lymphomas and leukemias J A M A *144* 1349, 1950

[142] PINEY, A AND RIACH, J. S. Multiple myeloma aleukemic and leukemic Folia Haemat *46* 37, 1931

[143] RAMIOUL, H . Le traitement du myélome multiple par la pentamidine Acta clin Belg *5* 523, 1950

[144] R

[145]

[146] REINER, M Application of electrophoresis to medical problems M Ann Distr Columbia *21* 11, 1952

[146a] REINER, M AND STERN K G Electrophoretic studies on the protein distribution in the serum of multiple myeloma patients Acta Haemat *9* 19, 1953

[147] REINHARD, E H , MOORE, C V , ...

[148] F

[149] ROHR, K , Maligne Knochen-und Knochenmarksneoplasien Schweiz Med. Wchnschr *77* 207, 1947.

[150] RORVIK, K Cryoglobulinemia Acta med Scandinav *137* 390, 1950

[151] ROSENTHAL, N AND VOGEL, P Value of the sternal puncture in the diagnosis of multiple myeloma J. Mt Sinai Hosp *4* 1001, 1938

[152] ROSENWASSER, H Plasmocytoma of the nasal cavity Laryngoscope *44* 826, 1934.

[153] RUBINSTEIN, M H Use of antimony in multiple myeloma Blood *4* 1068, 1949.

[154] RUNDLES, R. W , COOPER, G R , AND WILLETT, R W Multiple myeloma IV. Abnormal serum components and Bence-Jones protein J Clin. Investigation *30* 1125, 1951

[110] LOHLEIN, M Eisweisskristalle in den Harnkanälchen bei multiple Myeloma Beitr path Anat *69* 295, 1921

[111] LOWENHAUPT, E · Proliferative lesions in multiple myeloma with special reference to those of the spleen. Am J Path *21* 171, 1945

[112] LOW-BEER, B V A, LAWRENCE, J. H, AND STONE, R. S The therapeutic use of artificially produced radioactive substances Radiology *39* 573, 1942

[113] LUBARSCH, O Zur Myelomfrage Virchow's Archiv. *184* 213, 1906

[114] LUDIN, H Zur Kenntniss der Eiweissstoffwechselstorung beim Plasmocytom Schweiz med Wchnschr *77* 190, 1947

[114a] LUMB G AND PROSSER T. M. Plasma cell tumours J Bone & Joint Surg *30B* 124, 1948

[115] LUTTGENS, W AND BAYRD, E D Treatment of multiple myeloma with urethane. J A M A *147* 824, 1951

[116] MACINTYRE, W Case of mollities and fragilitas ossium accompanied with urine strongly charged with animal matter Med. Chir Soc. Tr *33* 211, 1850.

[117] MAGNUS-LEVY, A Multiple Myelome, Euglobulinämie Amyloidosis Zur Klinik und Pathologie der Amyloidosis Ztschr. f. klin Med *126* 62, 1933

[118] MAGNUS-LEVY, A Multiple myeloma XII Acta med Scandinav *95* 218, 1938.

[119] MAJERANOWSKI, JOHN F Subleukemic Plasma Cell Leukemia Arch. Path *53* 593, 1952

[120] MAJOOR, C L H Possibility of detecting individual proteins in blood serum by differentiation of solubility curves in concentrated sodium sulphate solutions Comparison of solubility curves with results of electrophoresis J. Biol Chem *169* 583, 1947

[121] MALLORY, T B Case Reports New England J. Med. *221* 986, 1939.

[122] MARCOVICI, E Report of case of primary multiple myeloma with Bence-Jones protein in pleural effusion Ann Int Med *2*.881, 1928.

[123] MARKHAM, J D, KRIZ, J R, AND WILLIAMS, J P Influence of stilbamidine in multiple myeloma with pre-existing renal involvement. Virginia M Monthly *76* 347, 1949

[124] MARTIN, N H A study of the plasma and tissue globulins in myelomatosis J Clin Investigation *26* 1189, 1947.

[125] MASSINI, R Untersuchung bei einem Falle von Bence-Jonesscher Krankheit Deutsches Arch f Klin Med *101* 29, 1911

[126] Medical Division of Merck and Co Inc Stilbamidine in the Treatment of Multiple Myeloma 1948

[127] MEYER, L M AND RUTZKY, J An unusual case of plasma-cell leukemia treated with a folic acid antagonist and urethane Cancer *4* 1043, 1951

[128] MEYLER, L Bence Jones proteinuria Arch Int Med *57* 708, 1936

[129] MILLER, J M, LONG, P H, AND SCHOENBACH, E B Successful Treatment of actinomycosis with stilbamidine J A M A *150* 35, 1952.

[130] MILNE, J Serum protein fractionation; comparison of sodium sulphate precipitations and electrophoresis. J Biol Chem *169* 595, 1947

[131] MOORE, D H., KABAT, E, AND GUTMAN, A. B Bence Jones proteinemia in multiple myeloma J Clin Investigation *22* 67, 1943

[132] NONNE, M Beitrag zur Klinik der Myelom-erkrankung der Wirbelsäule. Neurol. Centralbl *40* 1, 1921

[133] OHLER, R L, HOUGHTON, J. D, AND MOLONEY, W C · Urethane toxicity, report of a case of hepatic necrosis apparently due to urethane New England J. Med *243* 984, 1950

[134] OLHAGEN, B Spontaneous precipitation of crystalline globulin in myeloma serum

Scandinavian Congress of Internal Medicine, Copenhagen, June 27, 1948 Acta med Scandinav Supp *239* 86, 1950

[135] OLHAGEN, B : Modern analyses of blood protein Nord med. *34* 992, 1947

[136] OLHAGEN, B : On the correlation between the electrophoretic pattern and certain simple globulin reactions of human serum (the formol gel, Takata and Weltmann tests) Acta med Scandinav Supp *196* 478, 1947

[136a] OLHAGEN, B, THORELL, B, AND WISING, P The endocellular nucleic acid distribution and plasmaprotein formation in myelomatosis Scand J Clin Lab Investigation *1* 49, 1949

[137] OLIVER, J New directions in renal morphology, a method, its results, and its future Harvey Lectures *40* 102, 1944–45

[137a] PAIGE, B H A case of myeloma with unusual amyloid deposition Am J Path *7* 691, 1931

[138] PARISER, S, ZUCKER, R A, AND MEYER, L M Hematologic changes associated with the immune responses in man Acta med Scandinav *144* 201, 1952

[138a] PATTERSON, E, HADDOW, A, THOMAS, J A, AND WATKINSON, J M Leukaemia treated with urethane Lancet *250* 677, 1946

[139] PAUL, L W AND POHLE, E A Solitary myeloma of bone, review of roentgenologic features with report of 4 additional cases Radiology *35* 651, 1940.

[140] PEARSE, A G . The nature of Russell bodies and Kurloff bodies Observations on the cytochemistry of plasma cells and reticulum cells J Clin Path 2 81, 1949.

[141] PEARSON, O H AND ELIEL, L P. Use of ACTH and cortisone in lymphomas and leukemias J A.M A *144* 1349, 1950

[142] PINEY, A AND RIACH, J S · Multiple myeloma aleukemic and leukemic Folia Haemat *46* 37, 1931

[143] RAMIOUL, H Le traitement du myélome multiple par la pentamidine Acta clin Belg *5* 523, 1950

[144] REIMANN, H A Hyperproteinemia as a cause of autohemagglutination, observations in case of myeloma J A M A *99* 1411, 1932

[145] REIMANN, H. A. AND EKLUND, C M Long continued vaccine therapy as a cause of amyloidosis Am J M Sc *190* 88, 1935

[146] REINER, M Application of electrophoresis to medical problems M Ann Distr Columbia *21* 11, 1952

[146a] REINER, M AND STERN K. G Electrophoretic studies on the protein distribution in the serum of multiple myeloma patients Acta Haemat *9* 19, 1953

[147] REINHARD, E H, MOORE, C V, BIERBAUM, D S, AND MOORE, J Radioactive phosphorus as a therapeutic agent Review of literature and analysis of results of treatment of 155 patients with various blood dyscrasias, lymphomas and other malignant neoplastic diseases J Lab & Clin Med *31* 107, 1946

[148] ROBERTSON, T Plasmocytosis and hyperglobulinemia as manifestations of hypersensitivity Am J Med *9* 315, 1950.

[149] ROHR, K, Maligne Knochen-und Knochenmarksneoplasien Schweiz Med Wchnschr *77* 207, 1947

[150] RORVIK, K Cryoglobulinemia Acta med Scandinav *137* 390, 1950.

[151] ROSENTHAL, N AND VOGEL, P Value of the sternal puncture in the diagnosis of multiple myeloma J Mt. Sinai Hosp *4* 1001, 1938

[152] ROSEN[illegible]

[153] RUBIN[illegible]

[154] RUNDI[illegible]
Abr[illegible]
30 1125, 1951

[155] RUNDLES, R W, DILLON, M. L., AND DILLON, E. S.. Multiple myeloma. Effect of urethane therapy on plasma cell growth, abnormal serum protein components and Bence-Jones proteinuria J. Clin. Investigation 29.1243, 1950

[156] RUNDLES, R W AND REEVES, R J. Multiple myeloma II Variability of roentgen appearance and effect of urethane therapy on skeletal disease. Am J Roentgenol. 64.799, 1950.

[157] RUSSELL, W An address on a characteristic organism of cancer. Brit M J. 2 1356, 1890

[158] RUSTIZKY, J Multiple myeloma Deutsche. Ztschr. f. Chir. 3.162, 1873.

[159] SALTZMAN, A, TANG, Z., LIEBEN, F, AND SNAPPER, I: Urinary excretion of stilbamidine and 2-hydroxystilbamidine J Mt. Sinai Hosp 17·21, 1950

[160] SALTZMAN, F. AND BORGSTROM, H Multiple plasmocytoma treated with urethane. Acta med Scandinav. 136 388, 1950.

[161] SANDKÜHLER, S Das Heutige Bild des Plasmozytoms. Deutsche med. Wchnschr. 76 168, 1951

[162] SANDKUHLER, S Klinischer und elektrophoretischer Beitrag zur Kenntnis der Pathophysiologie des Plasmocytoms Deutsche med. Wchnschr 74 1563, 1949

[163] SCHEINKER, I.· Myelom und Nervensystem. Deutsche Ztschr. Nervenh 147·247, 1938

[164] SCHOENBACH, E. B, MILLER, J. M, GINSBERG, M, AND LONG, P H: Systemic Blastomycosis Treated with Stilbamidine J A M A 146.1317, 1951

[165] SCHOENBACH, E B. AND GREENSPAN, E M.. The pharmacology, mode of action and therapeutic potentialities of stilbamidine, pentamidine, propamidine, and other aromatic diamidines—a review Medicine 27 327, 1948

[166] SEEMANN, G Ein Fall von Plasma-zellulärem "Myelom" Centralbl f. allg. Path u path Anat 48 212, 1930

[167] SELIKOFF, I J AND BERNSTEIN, I J: Systemic reactions to the intravenous administration of Congo red Quart Bull Sea View Hosp 8 131, 1946

[168] SEN GUPTA, P C Observations on the neuropathic sequel of diamidino-stilbene therapy in kala azar Indian M Gaz 78 537, 1943

[169] SEN GUPTA, P C Hydroxystilbamidine in the treatment of Indian kala azar Indian M Gaz 85 547, 1950.

[170] SHENKIN, H A, HORN, R C, JR, AND GRANT, F. C. Lesions of the spinal extradural space producing cord compression Arch Surg 51 125, 1945

[171] SHIRER, J W., DUNCAN, W., AND HADEN, R. L.. Hyperproteinemia due to Bence Jones protein in myelomatosis Arch. Int. Med. 50 829, 1932

[172] SIKL, H A case of diffuse plasmocytosis with deposition of protein crystals in the kidneys J. Path. & Bact 61 149, 1949.

[173] SMITH, H W · The Kidney Structure and Function in Health and Disease, New York, Oxford University Press, 1951

[174] SNAPPER, I.· On the influence of stilbamidine on multiple myeloma J Mt Sinai Hosp 13 119, 1946.

[175] SNAPPER, I Stilbamidine and pentamidine in multiple myeloma J A.M.A., 133 157, 1947, 137 513, 1948.

[176] SNAPPER, I. Influence of 2-hydroxystilbamidine on the course of multiple myeloma J Mt Sinai Hosp. 15 156, 1948.

[177] SNAPPER, I.: Medical Clinics on Bone Disease. A Text and Atlas Ed. 2. New York, Interscience, 1949

[178] SNAPPER, I.. Rare Manifestations of Metabolic Bone Disease. Springfield, Ill, Charles C Thomas, 1952.

[179] Snapper, I · American muco-cutaneous leishmaniasis successfully treated with 2-hydroxystilbamidine. Am J Med *13* 665, 1952.

[180] Snapper, I, Lieben, F, Greenspan, E, and Schneid, B Determination of stilbamidine and 2-hydroxystilbamidine deposited in parenchymatous organs and tumors Cancer *4* 1246, 1951

[181] Snapper, I., Mirsky, S, Ris, H, Schneid, B and Rosenthal, M Development of inclusion bodies containing ribose nucleic acid in myeloma cells after injection of stilbamidine, determination of stilbamidine in myeloma tissue Blood *2* 311, 1947

[182] Snapper, I. and Schneid, B On the influence of stilbamidine upon myeloma cells. Blood *1*.534, 1946

[183] Snapper, I, Schneid, B, and Kurnick, N The presence of diamidines in myeloma cells after treatment with stilbamidine and 2-hydroxystilbamidine Acta Haemat *3* 129, 1950

[184] Snapper, I, Schneid, B, McVay, L, and Lieben, L Pharmacology and therapeutic value of diamidine derivatives—particularly of 2-hydroxystilbamidine. Tr New York Acad Sc *14* 269, 1952

[185] Snapper, I, Schneid, B, Lieben, F, Gerber, J, and Greenspan, E Influence of nucleic acid upon the fluorescence of nuclei and cytoplasm after injection of aromatic diamidines J Lab & Clin Med *37* 562, 1951

[186] Stark, A and Amidon, E L Diffuse plasma cell myelomatosis Arch Path *46* 183, 1948

[187] Stern, K G and Reiner, M Electrophoresis in medicine Yale J Biol & Med *19* 67, 1946

[188] Stewart, A and Weber, P Myelomatosis Quart. J Med *7* 211, 1938

[189] Stewart, M J and Taylor, A L Observations on solitary plasmocytoma J. Path & Bact *35* 541, 1932

[190] Tarr, L and Ferris, H W Multiple myeloma associated with nodular deposits of amyloid in the muscles and joints with Bence-Jones proteinuria Arch Int Med *64* 820, 1939

[191] Teilum, G Hyperglobulinemia, periarterial fibrosis of the spleen, and the wire loop lesions in disseminated lupus erythematosus in relation to allergic pathogenesis Am J Path *24* 409, 1948

[192] Tennent, W Plasmocytoma of bone Brit J Surg *32* 471, 1945

[192a] Ten Thije, O J Second Yearbook for Cancer Research in the Netherlands, 1952, p 194

[193] Thorn, G. W, Forsham, P H, Frawley, R F, Hill, S R, Roche, M, Stahelin, D, and Wilson, D L The clinical usefulness of ACTH and cortisone New England J Med *242* 824, 1950

[194] Thrower, W R and Valentine, F C O Propamidine in chronic wound sepsis Lancet *1*:133, 1943

[195] Tilden, I L Solitary myeloma of the skull Proc Staff Meet Clin, Honolulu 7 79, 1941

[195a] Trubowitz, S The sternal marrow aspiration of amyloid in multiple myeloma. Blood *5* 59, 585, 1950

[196] Udin, B and Putnam, F. W Investigation of Bence Jones protein, Federation Proceedings *10* 262, 1951

[197] [illegible]

1 675, 1901

[199] WALDENSTROM, J Die Fruhdiagnose der Myelomatose Acta chir. Scandinav 87 365, 1942.

[200] WALDENSTROM, J Incipient myelomatosis or essential hyperglobulinemia with fibrinopenia—a new syndrome? Acta med. Scandinav. *117*,216, 1944.

[201] WALDENSTROM, J Abnormal proteins in multiple myeloma, in: Advances in Internal Medicine, Chicago, Year Book Publishers, 1952, *vol* 5.

[202] WALDENSTROM, J Zwei Interessante Syndrome mit Hyperglobulinämie (Purpura Hyperglobulinämica oder Macroglobulinamia) Schweiz med Wchnschr. *78* 972, 1948

[203] WALLENIUS, G *Electrophoretic patterns of cerebrospinal fluid and serum compared* in normal and pathologic conditions Acta Soc Med Upsaliensis, New Series *57* 138, 1952

[204] WALLERSTEIN, R S Multiple myeloma without demonstrable bone lesions Am. J Med *10* 325, 1951

[205] WALLGREN, A Untersuchungen uber die Myelomkrankheit Upsala lakaref forh *25* 113, 1920

[206] WARBURG, O Über die Oxydationen in Lebenden Zellen nach Versuchen am Seeigelei *Ztschr f Physiol chem Strassb 66* 305, *1910.*

[207] WARREN, S The therapeutic use of radioactive phosphorus. Am J. M. Sc. *209* 701, 1945

[208] WEDER, C. Urethane in the treatment of multiple myeloma. Canad M A. J *62* 589, 1950

[209] WILLIAMS, H W Multiple myeloma of bone, report of two cases with remarks on the histogenesis Am J Cancer *16* 540, 1932

[210] WILSON, J D AND MILKMAN, L A Plasma cell myelomata of the skull and dura. Pennsylvania M J *35* 842, 1932

[211] WINTROBE, M M Clinical Hematology, Ed 2, Philadelphia, Lea and Febiger, 1946, p 779

[212] WINTROBE, M M AND BUELL, M V Hyperproteinemia associated with multiple *myeloma Bull Johns Hopkins Hosp 52 156, 1933*

[213] WORMS, R, LAUDAT, M, AND PACKER, J. Disparition transitoire de l'hyperglobulinémie au cours d'une maladie de Kahler traitée par la diamidine Sang *21* 73, 1950

[214] WRIGHT, J H *A case of multiple myeloma* Tr Assoc Am Phys *15*.137, 1900.

[215] WUHRMANN, F H, WUNDERLY, C, AND HASSIG, A Immunological investigations in ten cases of plasmocytoma Brit J. Exp Path *31* 507, 1951

[216] WUHRMANN, F, WUNDERLY, C, HASSIG, A, AND HUGENTOBLER, F Immunserologische *Untersuchungen über Paraproteine* Helvet M Acta. *16* 279, 1949

[217] WUHRMANN, F, WUNDERLY, C, AND HUGENTOBLER, F *Blood protein determinations* in 60 cases of plasmocytoma Deutsche med Wchnschr *16* 481, 1949

INDEX